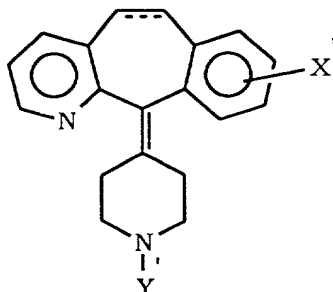


5 TRICYCLIC AMIDE AND UREA COMPOUNDS USEFUL FOR  
INHIBITION OF G-PROTEIN FUNCTION AND FOR TREATMENT  
OF PROLIFERATIVE DISEASES

BACKGROUND

International Publication Number WO92/11034, published July 9, 1992, discloses a method of increasing the sensitivity of a tumor to an antineoplastic agent, which tumor is resistant to the antineoplastic agent, by the concurrent administration of the antineoplastic agent and a potentiating agent of the formula:



15 wherein the dotted line represents an optional double bond, X' is hydrogen or halo, and Y' is hydrogen, substituted carboxylate or substituted sulfonyl. For example, Y' can be, amongst others, -COOR' wherein R' is C1 to C6 alkyl or substituted alkyl, phenyl, substituted phenyl, C7 to C12 aralkyl or substituted aralkyl or -2, -3, or -4 piperidyl or N-substituted piperidyl. Y' can also be, amongst others, SO<sub>2</sub>R' wherein R' is C1 to C6 alkyl, phenyl, substituted phenyl, C7 to C12 aralkyl or substituted aralkyl. Examples of such potentiating agents include 11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridines such as Loratadine.

25 Oncogenes frequently encode protein components of signal transduction pathways which lead to stimulation of cell growth and mitogenesis. Oncogene expression in cultured cells leads to cellular transformation, characterized by the ability of cells to grow in soft agar and the growth of cells as dense foci lacking the contact inhibition exhibited by non-transformed cells. Mutation and/or overexpression of certain  
 30 oncogenes is frequently associated with human cancer.

To acquire transforming potential, the precursor of the Ras oncoprotein must undergo farnesylation of the cysteine residue located in a carboxyl-terminal tetrapeptide. Inhibitors of the enzyme that catalyzes

this modification, farnesyl protein transferase, have therefore been suggested as anticancer agents for tumors in which Ras contributes to transformation. Mutated, oncogenic forms of ras are frequently found in many human cancers, most notably in more than 50% of colon and  
5 pancreatic carcinomas (Kohl et al., Science, Vol. 260, 1834 to 1837, 1993).

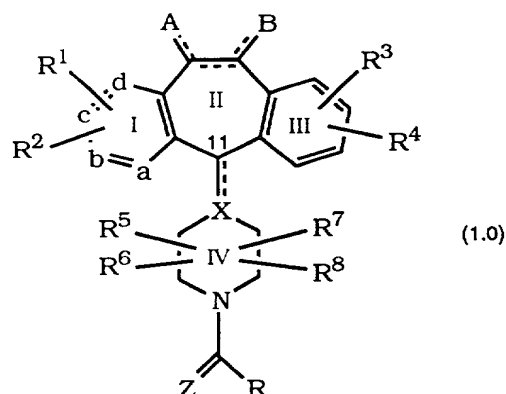
In view of the current interest in inhibitors of farnesyl protein transferase, a welcome contribution to the art would be compounds useful for the inhibition of farnesyl protein transferase. Such a contribution is  
10 provided by this invention.

#### SUMMARY OF THE INVENTION

Inhibition of farnesyl protein transferase by tricyclic compounds of this invention has not been reported previously. Thus, this invention  
15 provides a method for inhibiting farnesyl protein transferase using tricyclic compounds of this invention which: (i) potently inhibit farnesyl protein transferase, but not geranylgeranyl protein transferase I, *in vitro*; (ii) block the phenotypic change induced by a form of transforming Ras which is a farnesyl acceptor but not by a form of transforming Ras engineered to be a  
20 geranylgeranyl acceptor; (iii) block intracellular processing of Ras which is a farnesyl acceptor but not of Ras engineered to be a geranylgeranyl acceptor; and (iv) block abnormal cell growth in culture induced by transforming Ras. Several compounds of this invention have been demonstrated to have anti-tumor activity in animal models.

25 This invention provides a method for inhibiting the abnormal growth of cells, including transformed cells, by administering an effective amount of a compound of this invention. Abnormal growth of cells refers to cell growth independent of normal regulatory mechanisms (e.g., loss of contact inhibition). This includes the abnormal growth of: (1) tumor cells  
30 (tumors) expressing an activated Ras oncogene; (2) tumor cells in which the Ras protein is activated as a result of oncogenic mutation in another gene; and (3) benign and malignant cells of other proliferative diseases in which aberrant Ras activation occurs.

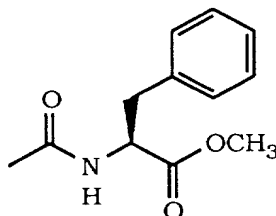
Compounds useful in the claimed methods are represented by  
35 Formula 1.0:



or a pharmaceutically acceptable salt or solvate thereof, wherein:

one of a, b, c and d represents N or NR<sup>9</sup> wherein R<sup>9</sup> is O<sup>-</sup>, -CH<sub>3</sub> or -(CH<sub>2</sub>)<sub>n</sub>CO<sub>2</sub>H wherein n is 1 to 3, and the remaining a, b, c and d groups represent CR<sup>1</sup> or CR<sup>2</sup>; or

- 5 each of a, b, c, and d are independently selected from CR<sup>1</sup> or CR<sup>2</sup>;  
 each R<sup>1</sup> and each R<sup>2</sup> is independently selected from H, halo, -CF<sub>3</sub>, -OR<sup>10</sup> (e.g., -OCH<sub>3</sub>), -COR<sup>10</sup>, -SR<sup>10</sup> (e.g., -SCH<sub>3</sub> and -SCH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>),  
 -S(O)<sub>t</sub>R<sup>11</sup> (wherein t is 0, 1 or 2, e.g., -SOCH<sub>3</sub> and -SO<sub>2</sub>CH<sub>3</sub>), -SCN,  
 10 -N(R<sup>10</sup>)<sub>2</sub>, -NR<sup>10</sup>R<sup>11</sup>, -NO<sub>2</sub>, -OC(O)R<sup>10</sup>, -CO<sub>2</sub>R<sup>10</sup>, -OCO<sub>2</sub>R<sup>11</sup>, -CN,  
 -NHC(O)R<sup>10</sup>, -NHCO<sub>2</sub>R<sup>10</sup>, -CONHR<sup>10</sup>, -CONHCH<sub>2</sub>CH<sub>2</sub>OH,  
 -NR<sup>10</sup>COOR<sup>11</sup>,



- SR<sup>11</sup>C(O)OR<sup>11</sup> (e.g., -SCH<sub>2</sub>CO<sub>2</sub>CH<sub>3</sub>), -SR<sup>11</sup>N(R<sup>75</sup>)<sub>2</sub> wherein each R<sup>75</sup>  
 15 is independently selected from H and -C(O)OR<sup>11</sup> (e.g.,  
 -S(CH<sub>2</sub>)<sub>2</sub>NHC(O)O-t-butyl and -S(CH<sub>2</sub>)<sub>2</sub>NH<sub>2</sub>), benzotriazol-1-yloxy,  
 tetrazol-5-ylthio, or substituted tetrazol-5-ylthio (e.g., alkyl substituted  
 tetrazol-5-ylthio such as 1-methyl-tetrazol-5-ylthio), alkynyl, alkenyl or  
 alkyl, said alkyl or alkenyl group optionally being substituted with halo,  
 20 -OR<sup>10</sup> or -CO<sub>2</sub>R<sup>10</sup>;

R<sup>3</sup> and R<sup>4</sup> are the same or different and each independently represents H, any of the substituents of R<sup>1</sup> and R<sup>2</sup>, or R<sup>3</sup> and R<sup>4</sup> taken together represent a saturated or unsaturated C<sub>5</sub>-C<sub>7</sub> fused ring to the benzene ring (Ring III);

$R^5$ ,  $R^6$ ,  $R^7$  and  $R^8$  each independently represents H,  $-CF_3$ ,  $-COR^{10}$ , alkyl or aryl, said alkyl or aryl optionally being substituted with  $-OR^{10}$ ,  $-SR^{10}$ ,  $-S(O)_tR^{11}$ ,  $-NR^{10}COOR^{11}$ ,  $-N(R^{10})_2$ ,  $-NO_2$ ,  $-COR^{10}$ ,  $-OCOR^{10}$ ,  $-OCO_2R^{11}$ ,  $-CO_2R^{10}$ ,  $OPO_3R^{10}$  or one of  $R^5$ ,  $R^6$ ,  $R^7$  and  $R^8$  can be taken in combination with  $R^{40}$  as defined below to represent  $-(CH_2)_r$  wherein r is 1 to 4 which can be substituted with lower alkyl, lower alkoxy,  $-CF_3$  or aryl, or  $R^5$  is combined with  $R^6$  to represent  $=O$  or  $=S$  and/or  $R^7$  is combined with  $R^8$  to represent  $=O$  or  $=S$ ;

$R^{10}$  represents H, alkyl, aryl, or aralkyl (e.g., benzyl);

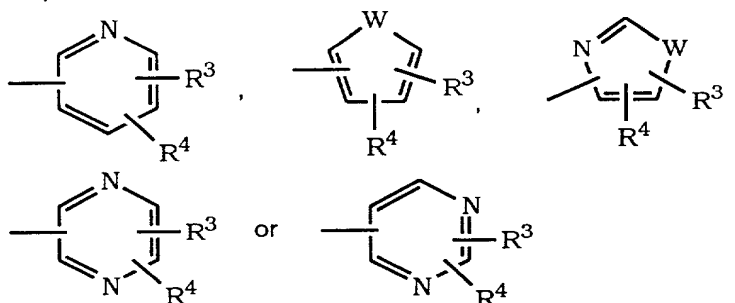
$R^{11}$  represents alkyl or aryl;

X represents N, CH or C, which C may contain an optional double bond (represented by the dotted line) to carbon atom 11;

the dotted line between carbon atoms 5 and 6 represents an optional double bond, such that when a double bond is present, A and B independently represent  $-R^{10}$ , halo,  $-OR^{11}$ ,  $-OCO_2R^{11}$  or  $-OC(O)R^{10}$ , and when no double bond is present between carbon atoms 5 and 6, A and B each independently represent  $H_2$ ,  $-(OR^{11})_2$ ; H and halo, dihalo, alkyl and H,  $(alkyl)_2$ ,  $-H$  and  $-OC(O)R^{10}$ , H and  $-OR^{10}$ ,  $=O$ , aryl and H,  $=NOR^{10}$  or  $-O-(CH_2)_p-O-$  wherein p is 2, 3 or 4;

R represents  $R^{40}$ ,  $R^{42}$ ,  $R^{44}$ , or  $R^{54}$ , as defined below;

$R^{40}$  represents H, aryl, alkyl, cycloalkyl, alkenyl, alkynyl or -D wherein -D represents



wherein  $R^3$  and  $R^4$  are as previously defined and W is O, S or  $NR^{10}$

wherein  $R^{10}$  is as defined above; said  $R^{40}$  cycloalkyl, alkenyl and alkynyl groups being optionally substituted with from 1-3 groups selected from halo,  $-CON(R^{10})_2$ , aryl,  $-CO_2R^{10}$ ,  $-OR^{12}$ ,  $-SR^{12}$ ,  $-N(R^{10})_2$ ,

$-N(R^{10})CO_2R^{11}$ ,  $-COR^{12}$ ,  $-NO_2$  or D, wherein -D,  $R^{10}$  and  $R^{11}$  are as defined above and  $R^{12}$  represents  $R^{10}$ ,  $-(CH_2)_mOR^{10}$  or  $-(CH_2)_qCO_2R^{10}$

wherein  $R^{10}$  is as previously defined, m is 1 to 4 and q is 0 to 4; said alkenyl and alkynyl  $R^{40}$  groups not containing  $-OH$ ,  $-SH$  or



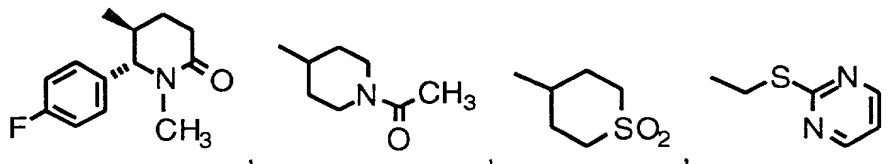
-N(R<sup>10</sup>)<sub>2</sub> on a carbon containing a double or triple bond respectively; or

R<sup>40</sup> represents phenyl substituted with a group selected from

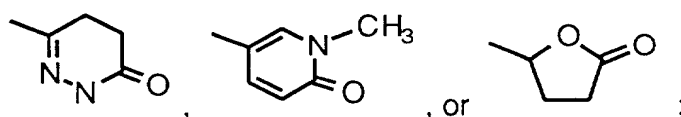
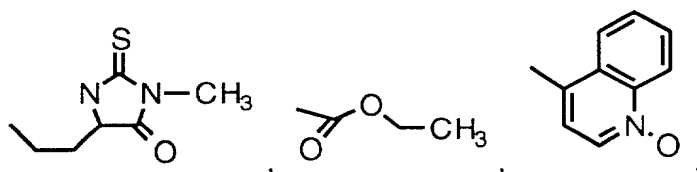
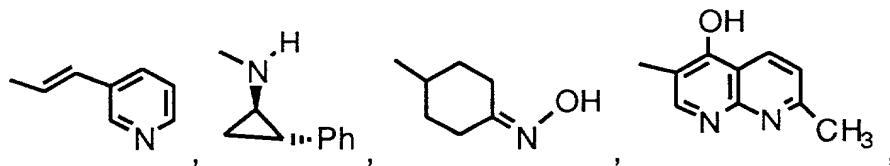
-SO<sub>2</sub>NH<sub>2</sub>, -NHSO<sub>2</sub>CH<sub>3</sub>, -SO<sub>2</sub>NHCH<sub>3</sub>, -SO<sub>2</sub>CH<sub>3</sub>, -SOCH<sub>3</sub>, -SCH<sub>3</sub>, or -NHSO<sub>2</sub>CF<sub>3</sub>, preferably, said group is located in the para (p-) position of

5 the phenyl ring; or

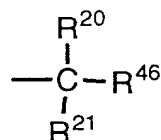
R<sup>40</sup> represents a group selected from



10



R<sup>42</sup> represents

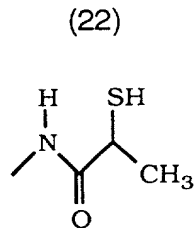
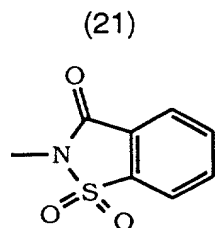
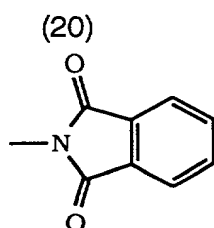


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wherein R<sup>20</sup>, R<sup>21</sup> and R<sup>46</sup> are each independently selected from the group consisting of:

- (1) H;
  - (2) -(CH<sub>2</sub>)<sub>q</sub>SC(O)CH<sub>3</sub> wherein q is 1 to 3 (e.g., -CH<sub>2</sub>SC(O)CH<sub>3</sub>);
  - 20 (3) -(CH<sub>2</sub>)<sub>q</sub>OSO<sub>2</sub>CH<sub>3</sub> wherein q is 1 to 3 (e.g., -CH<sub>2</sub>OSO<sub>2</sub>CH<sub>3</sub>);
  - (4) -OH;
  - (5) -CS(CH<sub>2</sub>)<sub>w</sub>(substituted phenyl) wherein w is 1 to 3 and the
- substitutents on said substituted phenyl group are the same substitutents as described below for said substituted phenyl (e.g., -C-S-CH<sub>2</sub>-4-
- 25 methoxyphenyl);

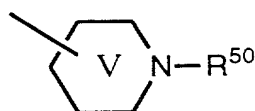
- (6)  $\text{-NH}_2$ ;
- (7)  $\text{-NHCBZ}$  (wherein CBZ stands for carbonylbenzyloxy--i.e., CBZ represents  $\text{-C(O)OCH}_2\text{C}_6\text{H}_5$ );
- 5 (8)  $\text{-NHC(O)OR}^{22}$  wherein  $\text{R}^{22}$  is an alkyl group having from 1 to 5 carbon atoms (e.g.,  $\text{R}^{22}$  is t-butyl thus forming  $\text{-NHBOC}$  wherein BOC stands for tert-butyloxycarbonyl--i.e., BOC represents  $\text{-C(O)OC(CH}_3)_3$ ), or  $\text{R}^{22}$  represents phenyl substituted with 1 to 3 alkyl groups (e.g., 4-methylphenyl);
- (9) alkyl (e.g., ethyl);
- 10 (10)  $\text{-(CH}_2)_k\text{phenyl}$  wherein k is 1 to 6, usually 1 to 4 and preferably 1 (e.g., benzyl);
- (11) phenyl;
- (12) substituted phenyl (i.e., phenyl substituted with from 1 to 3 substituents, preferably one) wherein the substituents are selected from
- 15 the group consisting of: halo (e.g., Br, Cl, or I, with Br being preferred);  $\text{NO}_2$ ;  $\text{-OH}$ ;  $\text{-OCH}_3$ ;  $\text{-NH}_2$ ;  $\text{-NHR}^{22}$ ;  $\text{-N(R}^{22})_2$ ; alkyl (e.g., alkyl having from 1 to 3 carbons with methyl being preferred);  $\text{-O(CH}_2)_t\text{phenyl}$  (wherein t is from 1 to 3 with 1 being preferred); and  $\text{-O(CH}_2)_t\text{substituted phenyl}$  (wherein t is from 1 to 3 with 1 being preferred); examples of substituted
- 20 phenyls include, but are not limited to, p-bromophenyl, m-nitrophenyl, o-nitrophenyl, m-hydroxy-phenyl, o-hydroxyphenyl, methoxyphenyl, p-methylphenyl, m-methyl-phenyl, and  $\text{-OCH}_2\text{C}_6\text{H}_5$ ;
- (13) naphthyl;
- (14) substituted naphthyl, wherein the substituents are as defined
- 25 for substituted phenyl above;
- (15) bridged polycyclic hydrocarbons having from 5 to 10 carbon atoms (e.g., adamantyl and norbornyl);
- (16) cycloalkyl having from 5 to 7 carbon atoms (e.g., cyclopentyl, and cyclohexyl);
- 30 (17) heteroaryl (e.g., pyridyl, and pyridyl N-oxide);
- (18) hydroxyalkyl (e.g.,  $\text{-(CH}_2)_v\text{OH}$  wherein v is 1 to 3, such as, for example,  $\text{-CH}_2\text{OH}$ );
- (19) substituted pyridyl or substituted pyridyl N-oxide wherein the substituents are selected from methylpyridyl, morpholinyl, imidazolyl,
- 35 1-piperidinyl, 1-(4-methylpiperazinyl),  $\text{-S(O)}_t\text{R}^{11}$ , or any of the substituents given above for said substituted phenyl, and said substituents are bound to a ring carbon by replacement of the hydrogen bound to said carbon;



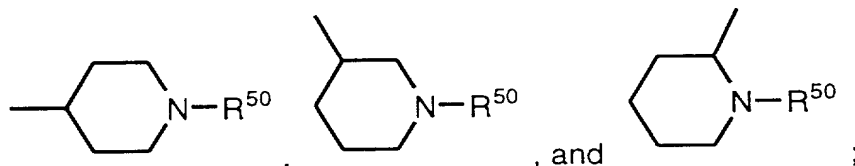
(23)  $-\text{NHC(O)}-(\text{CH}_2)_k\text{-phenyl}$  or  $-\text{NH(O)}-(\text{CH}_2)_k\text{-substituted phenyl}$ ,  
wherein said k is as defined above (i.e., 1-6, usually 1-4 and preferably

5 1);

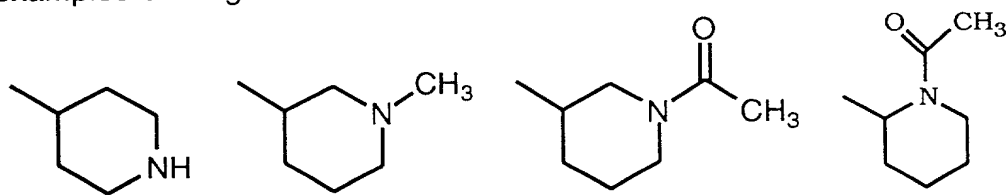
(24) piperidine Ring V:



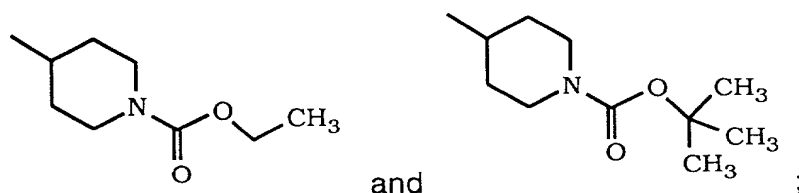
wherein  $\text{R}^{50}$  represents H, alkyl (e.g., methyl), alkylcarbonyl (e.g.,  $\text{CH}_3\text{C(O)-}$ ), alkyloxycarbonyl (e.g.,  $-\text{C(O)O-t-C}_4\text{H}_9$ ,  $-\text{C(O)OC}_2\text{H}_5$ , and  $-\text{C(O)OCH}_3$ ), haloalkyl (e.g., trifluoromethyl), or  $-\text{C(O)NH(R}^{10})$  wherein  $\text{R}^{10}$  is H or alkyl; Ring V includes



examples of Ring V include:



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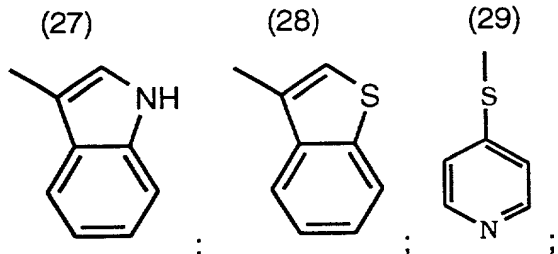


and

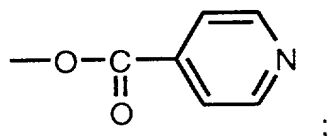
(25)  $-\text{NHC(O)CH}_2\text{C}_6\text{H}_5$  or  $-\text{NHC(O)CH}_2\text{-substituted-C}_6\text{H}_5$ , for  
example  $-\text{NHC(O)CH}_2\text{-p-hydroxyphenyl}$ ,  $-\text{NHC(O)CH}_2\text{-m-hydroxyphenyl}$ ,  
and  $-\text{NHC(O)CH}_2\text{-o-hydroxyphenyl}$ ;

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(26)  $-\text{NHC(O)OC}_6\text{H}_5$ ;



(30) -OC(O)-heteroaryl, for example

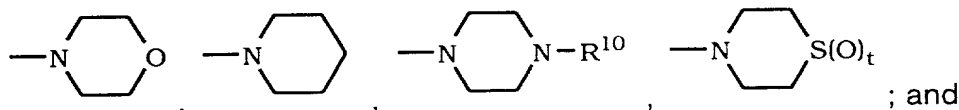


5 (31) -O-alkyl (e.g., -OCH<sub>3</sub>);

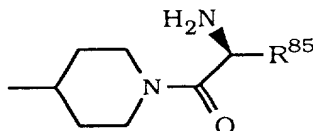
(32) -CF<sub>3</sub>;

(33) -CN;

(34) a heterocycloalkyl group of the formula



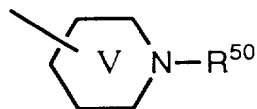
10 (35) a piperidinyll group of the formula



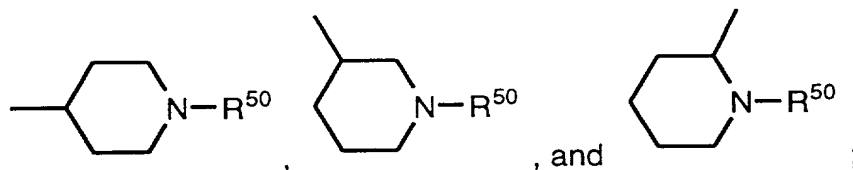
wherein R<sup>85</sup> is H, alkyl, or alkyl substituted by -OH or -SCH<sub>3</sub> ; or

R<sup>20</sup> and R<sup>21</sup> taken together form a =O group and the remaining R<sup>46</sup> is as defined above; or

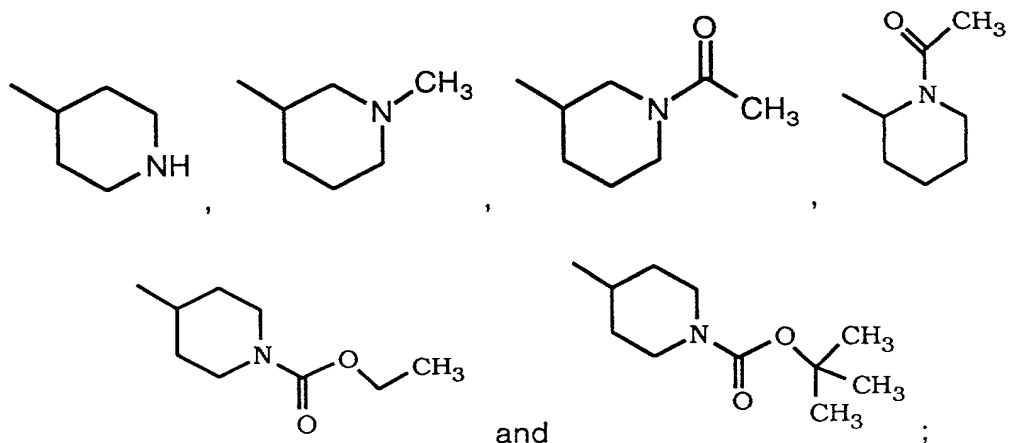
15 Two of R<sup>20</sup>, R<sup>21</sup> and R<sup>46</sup> taken together form piperidine Ring V



wherein R<sup>50</sup> represents H, alkyl (e.g., methyl), alkylcarbonyl (e.g., CH<sub>3</sub>C(O)-), alkyloxycarbonyl (e.g., -C(O)O-t-C<sub>4</sub>H<sub>9</sub>, -C(O)OC<sub>2</sub>H<sub>5</sub>, and -C(O)OCH<sub>3</sub>), haloalkyl (e.g., trifluoro-methyl), or -C(O)NH(R<sup>10</sup>) wherein R<sup>10</sup> is H or alkyl; Ring V includes

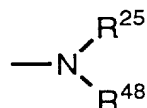


examples of Ring V include:



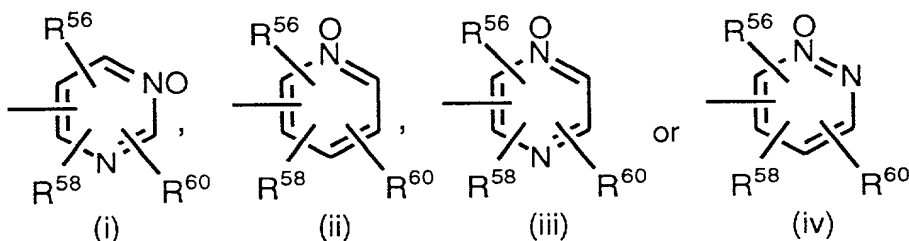
- 5 with the proviso  $R^{46}$ ,  $R^{20}$ , and  $R^{21}$  are selected such that the carbon atom to which they are bound does not contain more than one heteroatom (i.e.,  $R^{46}$ ,  $R^{20}$ , and  $R^{21}$  are selected such that the carbon atom to which they are bound contains 0 or 1 heteroatom);

$R^{44}$  represents



- 10 wherein  $R^{25}$  represents heteroaryl (e.g., pyridyl or pyridyl N-oxide), N-methylpiperidinyll or aryl (e.g., phenyl and substituted phenyl); and  $R^{48}$  represents H or alkyl (e.g., methyl);

$R^{54}$  represents an N-oxide heterocyclic group of the formula (i), (ii), (iii) or (iv):

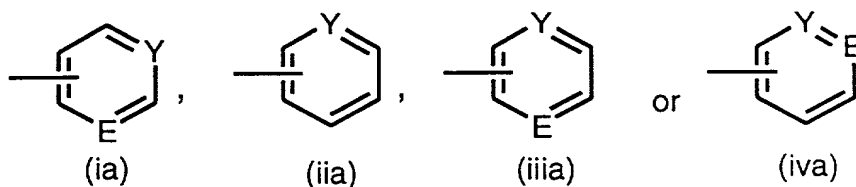


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wherein  $R^{56}$ ,  $R^{58}$ , and  $R^{60}$  are the same or different and each is independently selected from H, halo,  $-CF_3$ ,  $-OR^{10}$ ,  $-C(O)R^{10}$ ,  $-SR^{10}$ ,  $-S(O)_eR^{11}$  (wherein e is 1 or 2),  $-N(R^{10})_2$ ,  $-NO_2$ ,  $-CO_2R^{10}$ ,  $-OCO_2R^{11}$ ,  $-OCOR^{10}$ , alkyl, aryl, alkenyl or alkynyl, which alkyl may be substituted with  $-OR^{10}$ ,  $-SR^{10}$  or  $-N(R^{10})_2$  and which alkenyl may be substituted with  $OR^{11}$  or  $SR^{11}$ ; or

20

$R^{54}$  represents an N-oxide heterocyclic group of the formula (ia), (iia), (iiaa) or (iva):

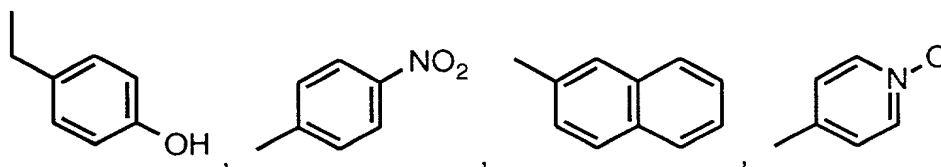
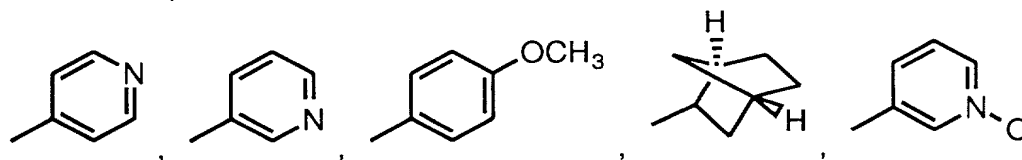


wherein Y represents N<sup>+</sup>-O<sup>-</sup> and E represents N; or

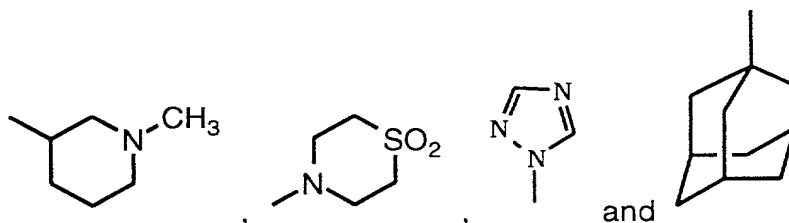
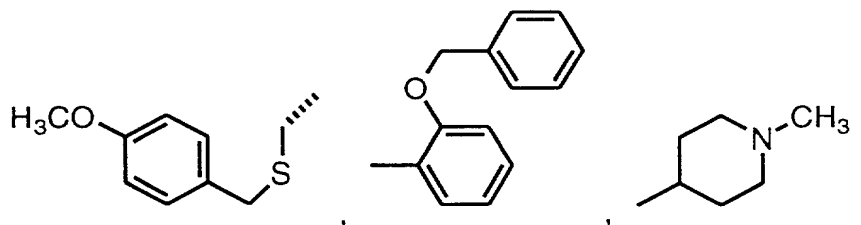
R<sup>54</sup> represents an alkyl group substituted with one of said N-oxide heterocyclic groups (i), (ii), (iii), (iv), (ia), (iia), (iiia) or (iva);

5 Z represents O or S such that R can be taken in combination with R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> or R<sup>8</sup> as defined above, or R represents R<sup>40</sup>, R<sup>42</sup>, R<sup>44</sup> or R<sup>54</sup>.

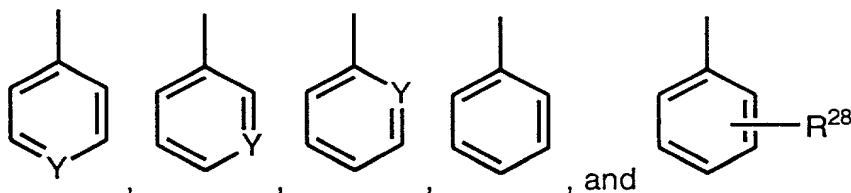
Examples of R<sup>20</sup>, R<sup>21</sup>, and R<sup>46</sup> for the above formulas include:



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Examples of R<sup>25</sup> groups include:

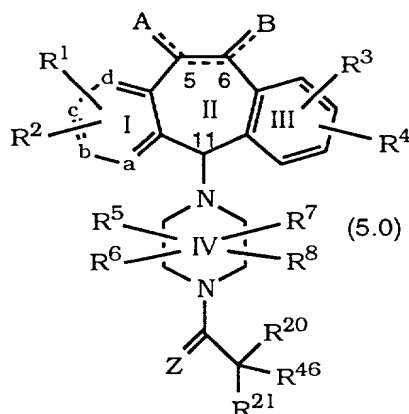


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wherein Y represents N or NO, R<sup>28</sup> is selected from the group consisting of: C<sub>1</sub> to C<sub>4</sub> alkyl, halo, hydroxy, NO<sub>2</sub>, amino (-NH<sub>2</sub>), -NHR<sup>30</sup>, and -N(R<sup>30</sup>)<sub>2</sub> wherein R<sup>30</sup> represents C<sub>1</sub> to C<sub>6</sub> alkyl.

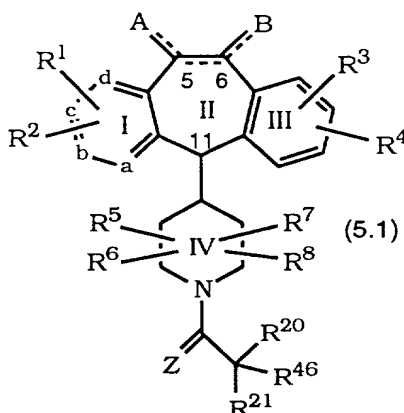
Tricyclic compounds useful in the methods of this invention are described in: (1) U.S. 5,151,423; (2) U.S. 4,826,853; (3) U.S. 5,089,496; (4) WO 88/03138 published on May 5, 1988 (PCT/US87/02777); and (5) U.S. 5,104,876; the disclosures of each being incorporated herein by reference thereto. Those compounds within the scope of this invention which are not described in these documents are described herein.

This invention also provides novel compounds of Formula 1.0 having the formula:



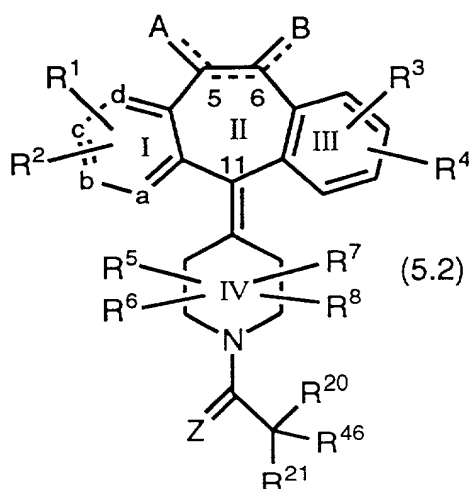
wherein all substituents are as defined for Formula 1.0

This invention further provides novel compounds of Formula 1.0 having the formula:



wherein all substituents are as defined for Formula 1.0

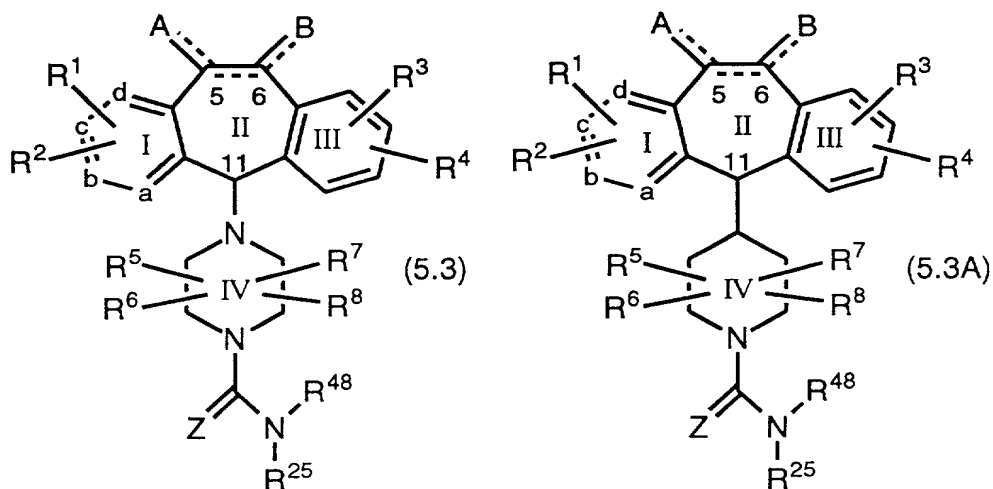
Additionally, this invention provides novel compounds of Formula 1.0 having the formula:



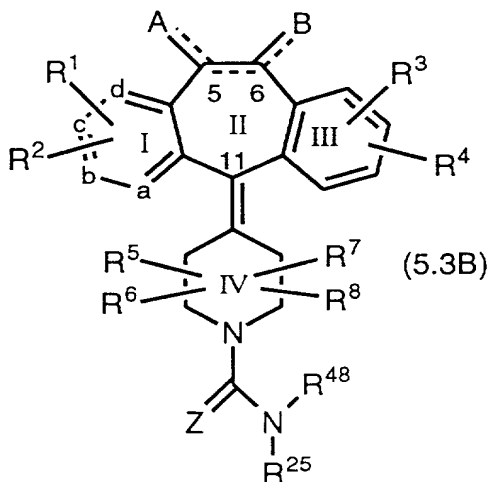
wherein all substituents are as defined for Formula 1.0.

- Compounds of Formula 5.2 include compounds wherein the substituents R<sup>20</sup>, R<sup>21</sup>, and R<sup>46</sup> are selected such that when one of said substituents R<sup>20</sup>, R<sup>21</sup>, and R<sup>46</sup> (e.g., R<sup>46</sup>) is selected from the group consisting of: (1) H, (2) -OH, (3) -NH<sub>2</sub>, (4) -NHC(O)OR<sup>22</sup>, (5) alkyl, (6) phenyl, (7) heteroaryl, (8) hydroxyalkyl, (9) substituted pyridyl, (10) substituted phenyl and (11) -O-alkyl, then the remaining two of said substituents R<sup>20</sup>, R<sup>21</sup> and R<sup>46</sup> (e.g., R<sup>20</sup> and R<sup>21</sup>) cannot both be H when:
- (a) R<sup>1</sup> and R<sup>2</sup> are both H, and (b) the double bond between C-5 and C-6 is absent, and (c) both A and B are H<sub>2</sub>, and (d) R<sup>4</sup> is H, and (e) R<sup>3</sup> is H or Cl at C-8. Compounds of Formula 5.2 also include compounds wherein when R<sup>46</sup> is a group (1) to (11) defined above then R<sup>20</sup> and R<sup>21</sup> cannot both be H when: R<sup>1</sup> and R<sup>2</sup> are both H, and both A and B are H or H<sub>2</sub>.
- Compounds of Formula 5.2 further include compounds wherein when R<sup>46</sup> is a group (1) to (11) defined above then R<sup>20</sup> and R<sup>21</sup> cannot both be H when R<sup>1</sup> and R<sup>2</sup> are both H. Compounds of Formula 5.2 also include compounds wherein two of R<sup>20</sup>, R<sup>21</sup> and R<sup>46</sup> are not H when R<sup>1</sup> and R<sup>2</sup> are both H.
- This invention further provides novel compounds of Formula 1.0 having the formula:



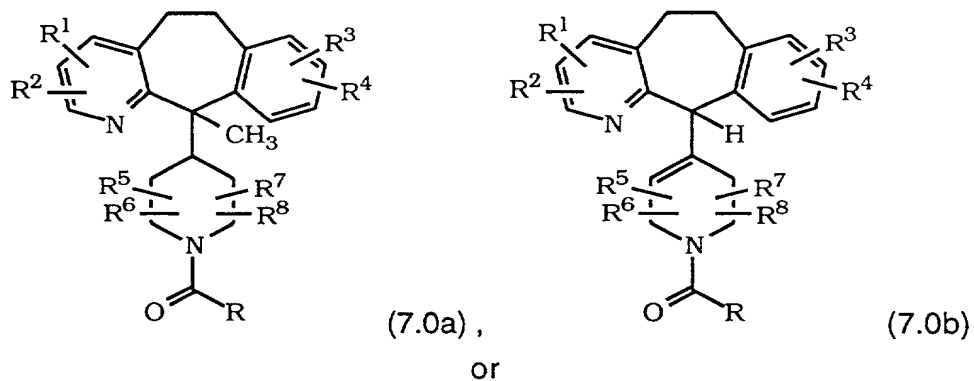


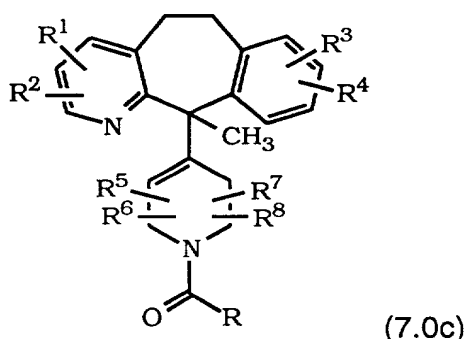
or



wherein all the substituents are as defined for Formula 1.0. Preferably R<sup>25</sup> represents heteroaryl.

This invention also provides novel compounds of the formula 7.0 having the formula:





wherein R, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> and R<sup>8</sup> are as defined above for compounds of the formula 1.0, which compounds are useful in the methods claimed herein.

5 This invention also provides a method for inhibiting tumor growth by administering an effective amount of the tricyclic compounds, described herein, to a mammal (e.g., a human) in need of such treatment. In particular, this invention provides a method for inhibiting the growth of tumors expressing an activated Ras oncogene by the administration of an

10 effective amount of the above described compounds. Examples of tumors which may be inhibited include, but are not limited to, lung cancer (e.g., lung adenocarcinoma), pancreatic cancers (e.g., pancreatic carcinoma such as, for example, exocrine pancreatic carcinoma), colon cancers (e.g., colorectal carcinomas, such as, for example, colon adenocarcinoma and colon adenoma), myeloid leukemias (for example, acute myelogenous leukemia (AML)), thyroid follicular cancer, myelodysplastic syndrome

15 (MDS), bladder carcinoma and epidermal carcinoma.

It is believed that this invention also provides a method for inhibiting proliferative diseases, both benign and malignant, wherein Ras proteins

20 are aberrantly activated as a result of oncogenic mutation in other genes-- i.e., the Ras gene itself is not activated by mutation to an oncogenic form-- with said inhibition being accomplished by the administration of an effective amount of the tricyclic compounds described herein, to a mammal (e.g., a human) in need of such treatment. For example, the

25 benign proliferative disorder neurofibromatosis, or tumors in which Ras is activated due to mutation or overexpression of tyrosine kinase oncogenes (e.g., neu, src, abl, lck, and fyn), may be inhibited by the tricyclic compounds described herein.

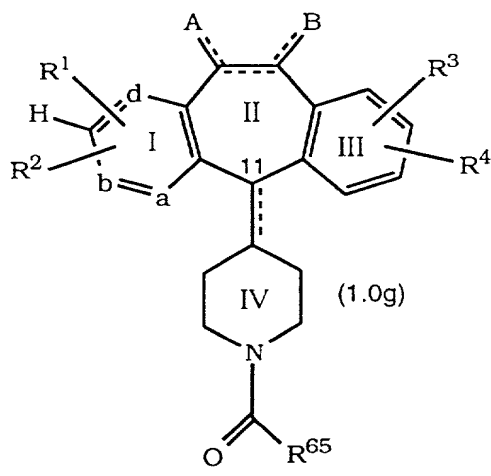
The compounds of this invention inhibit farnesyl protein transferase

30 and the farnesylation of the oncogene protein Ras. This invention further provides a method of inhibiting ras farnesyl protein transferase, in

mammals, especially humans, by the administration of an effective amount of the tricyclic compounds described above. The administration of the compounds of this invention to patients, to inhibit farnesyl protein transferase, is useful in the treatment of the cancers described above.

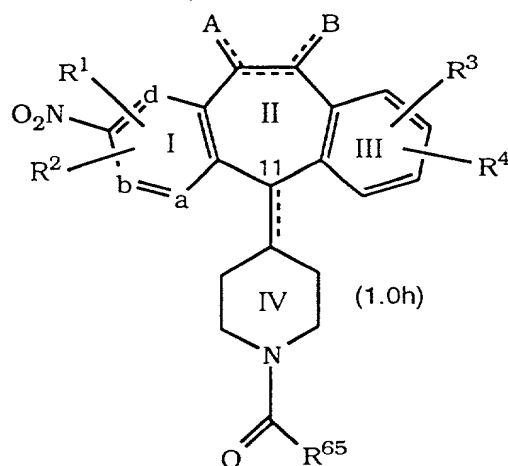
5 The tricyclic compounds useful in the methods of this invention inhibit the abnormal growth of cells. Without wishing to be bound by theory, it is believed that these compounds may function through the inhibition of G-protein function, such as ras p21, by blocking G-protein isoprenylation, thus making them useful in the treatment of proliferative  
10 diseases such as tumor growth and cancer. Without wishing to be bound by theory, it is believed that these compounds inhibit ras farnesyl protein transferase, and thus show antiproliferative activity against ras transformed cells.

This invention also provides a process for producing 3-nitro substituted compounds. The process comprises reacting one molar  
15 equivalent of a compound:



wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, A, B, a, b, d, and the dotted lines are as defined for  
20 Formula 1.0; and R<sup>65</sup> represents H or -OR<sup>66</sup> wherein R<sup>66</sup> represents alkyl (e.g., C<sub>1</sub> to C<sub>4</sub> alkyl, preferably ethyl); with one molar equivalent of a nitrating reagent, said nitrating reagent being preformed (i.e., prepared first) by mixing, at cold temperature (e.g., at 0°C) equimolar amounts of tetrabutyl ammonium nitrate with TFAA; the reaction of the nitrating reagent with the compound of Formula 1.0g taking place in a suitable  
25 aprotic solvent (e.g., CH<sub>2</sub>Cl<sub>2</sub>, CHCl<sub>3</sub>, toluene or THF); said reaction with said nitrating reagent being conducted at a temperature and for a period of time sufficient to allow the reaction to proceed at a reasonable rate to produce the desired final 3-nitro compound of Formula 1.0h (described

below)--i.e., the reaction of the compound of Formula 1.0g with said nitrating reagent is conducted at an initial temperature of 0°C, and said reaction temperature is thereafter allowed to rise to about 25°C during the reaction time period. The reaction usually proceeds overnight to completion, i.e., the reaction usually proceeds for about 16 hours. The reaction can be conducted within a temperature of 0°C to about 25°C during a time period of about 10 to about 24 hours. Preferably the reaction is initially conducted at 0°C and the temperature is allowed to warm up to 25°C. The reaction produces the 3-nitro compound (1.0h):

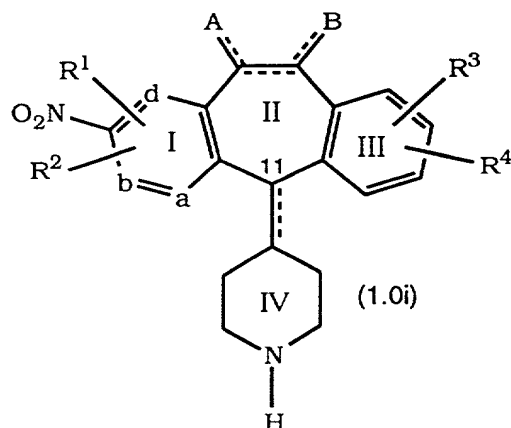


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The compound of Formula 1.0h can then be converted to other 3-substituted products by methods well known to those skilled in the art. For example, the 3-nitro compounds can be converted to 3-amino, 3-halo, 3-cyano, 3-alkyl, 3-aryl, 3-thio, 3-arylalkyl, 3-hydroxyl, and 3-OR<sup>67</sup> wherein R<sup>67</sup> is alkyl or aryl. The 3-substituted compounds can then be converted to final products (wherein R<sup>65</sup> is R<sup>42</sup> or R<sup>44</sup>) by the procedures described herein.

15

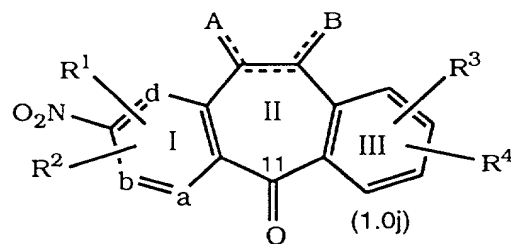
This invention also provides a process for producing 3-nitro compounds of the formula (1.0i):



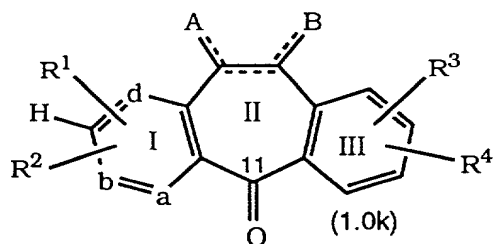
by producing a compound of Formula 1.0h from 1.0g as described above;  
and then hydrolyzing the compound of Formula 1.0h by dissolving the  
compound of Formula 1.0h in a sufficient amount of concentrated acid  
5 (e.g., concentrated HCl or aqueous sulfuric acid), and heating the  
resulting mixture to a temperature sufficient to remove (hydrolyze) the  
-C(O)R<sup>65</sup> substituent, for example, heating to reflux or to a temperature of  
about 100°C. This hydrolysis process is exemplified in Preparative  
Example 28.

10 The compound of Formula 1.0i can then be converted to other 3-  
substituted compounds as discussed above for the compounds of Formula  
1.0h. The compounds of Formula 1.0i can then be converted to  
compounds of this invention by the methods described herein.

This invention also provides a process for producing compounds of  
15 the formula (1.0j):



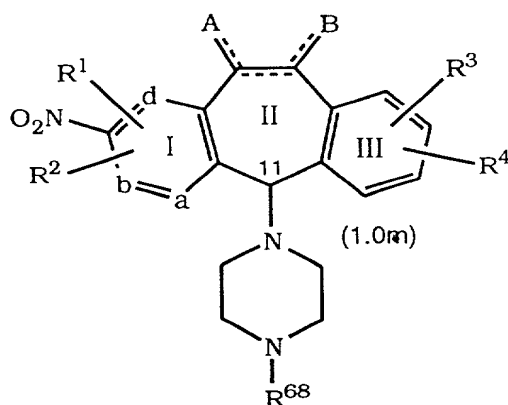
by reacting one molar equivalent a compound of formula (1.0k):



with one molar equivalent of a nitrating reagent, said nitrating reagent being preformed (i.e., prepared first) by mixing, at cold temperature (e.g., at 0°C) equimolar amounts of tetrabutyl ammonium nitrate with TFAA; the reaction of the nitrating reagent with the compound of Formula 1.0k taking place in a suitable aprotic solvent (e.g., CH<sub>2</sub>Cl<sub>2</sub>, CHCl<sub>3</sub>, toluene or THF); said reaction with said nitrating reagent being conducted at a temperature and for a period of time sufficient to allow the reaction to proceed at a reasonable rate to produce the desired final 3-nitro compound of Formula 1.0j--i.e., the reaction of the compound of Formula 1.0k with said nitrating reagent is conducted at an initial temperature of 0°C, and said reaction temperature is thereafter allowed to rise to about 25°C during the reaction time period. The reaction usually proceeds overnight to completion, i.e., the reaction usually proceeds for about 16 hours. The reaction can be conducted within a temperature of 0°C to about 25°C during a time period of about 10 to about 24 hours. Preferably the reaction is initially conducted at 0°C and the temperature is allowed to warm up to 25°C. In Formulas 1.0j and 1.0k, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, A, B, a, b, d, and the dotted lines are as defined for Formula 1.0

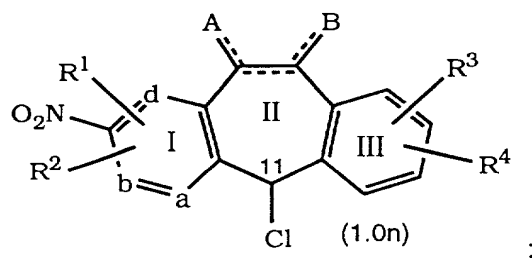
The compounds of Formula 1.0j can be converted to compounds of Formula 1.0h by methods described below. Also, as discussed above for the compounds of Formula 1.0h, the compounds of Formula 1.0j can be converted to other 3-substituted compounds wherein the substituents are those discussed above for Formula 1.0h.

The compounds of Formula 1.0j can be converted to compounds of Formula 1.0m:

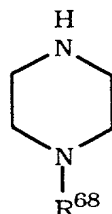


wherein R<sup>68</sup> is H or -COOR<sup>a</sup> wherein R<sup>a</sup> is a C<sub>1</sub> to C<sub>3</sub> alkyl group (preferably R<sup>68</sup> is H), by reducing a compound of Formula 1.0j with a suitable reducing agent (such as sodium borohydride) in a suitable

- solvent (such as EtOH or MeOH) at a suitable temperature to allow the reaction to proceed at a reasonable rate (e.g., 0 to about 25°C); reacting the resulting product (Formula 1.0j wherein the =O has been reduced to a -OH) with a chlorinating agent (e.g., thionyl chloride) in an suitable organic solvent (e.g., benzene, toluene or pyridine) at a suitable temperature to allow the reaction to proceed at a reasonable rate (e.g., about -20 to about 20°C, preferably at -15°C, see, for example Preparative Example 7) to produce a compound of Formula 1.0n:



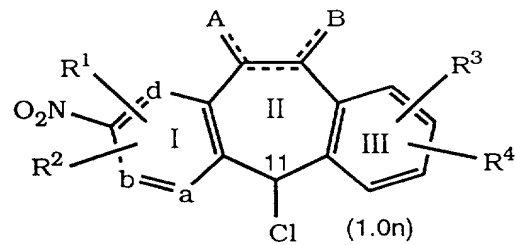
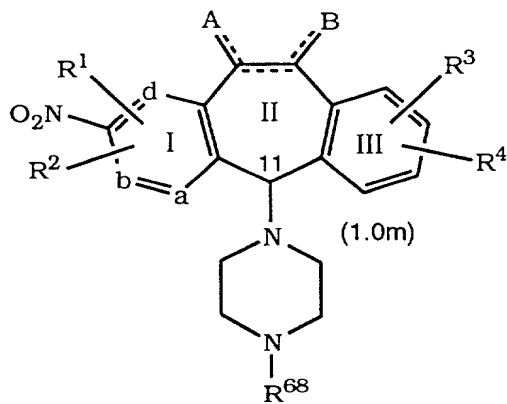
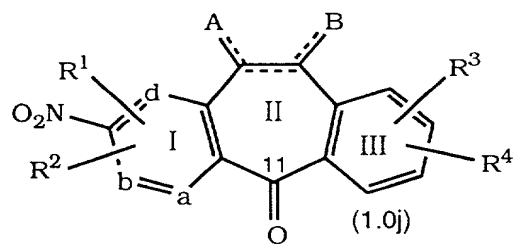
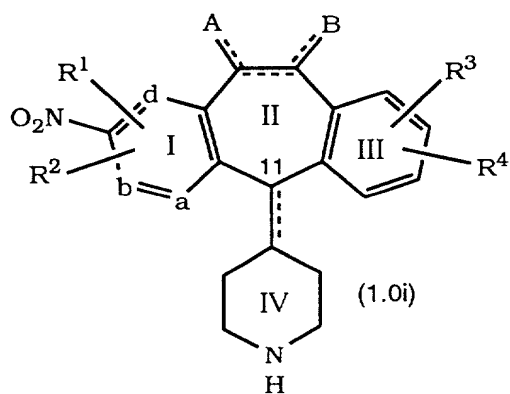
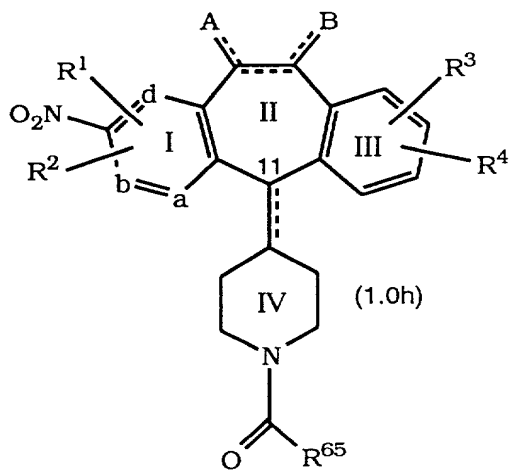
- and reacting a compound of Formula 1.0n with a compound of the formula:



- wherein  $R^{68}$  is as previously defined, and is preferably H, in a suitable organic solvent (such as THF or toluene) containing a suitable base (such as  $Et_3N$  or N-methylmorpholine) at a suitable temperature to allow the reaction to proceed at a reasonable rate (e.g., 25 to about 120°C).

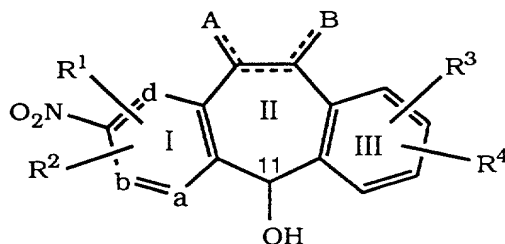
- Compounds of Formula 1.0m can be converted to compounds of this invention by the methods disclosed herein. Also, as discussed above for the compounds of Formula 1.0h, the compounds of Formula 1.0m can be converted to other 3-substituted compounds wherein the substituents are those discussed above for Formula 1.0h.

This invention also provides novel compounds (produced in the above described processes as intermediates to the compounds of this invention) having the formulas:



and

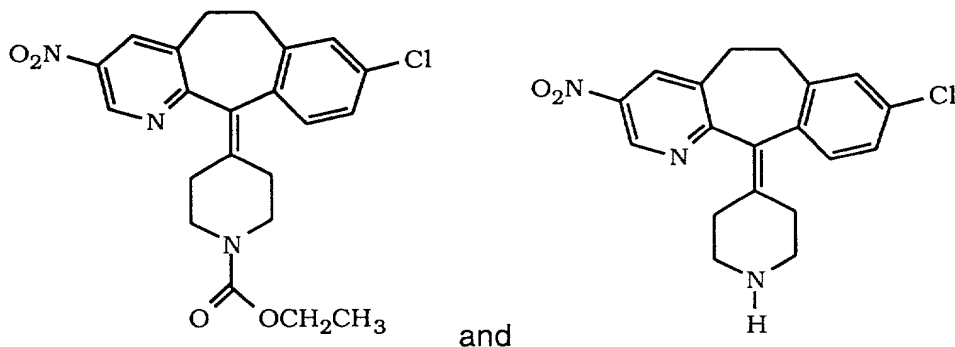




wherein all substituents are as defined herein.

Preferably, for the intermediate compounds of the processes of this invention, R<sup>1</sup> and R<sup>2</sup> are H; R<sup>3</sup> is halo, most preferably Cl, in the C-8 position; R<sup>4</sup> is H; and A and B are H when the double between C-5 and C-6 is present, and A and B are H<sub>2</sub> when the bond between C-5 and C-6 is a single bond (most preferably the bond between C-5 and C-6 is a single bond). Those skilled in the art will appreciate that Rings I, II, and/or III can be further substituted, as described herein, to produce the desired compounds of the invention.

Examples of such novel intermediate compounds include:



## DETAILED DESCRIPTION OF THE INVENTION

As used herein, the following terms are used as defined below unless otherwise indicated:

M<sup>+</sup>-represents the molecular ion of the molecule in the mass spectrum;

MH<sup>+</sup>-represents the molecular ion plus hydrogen of the molecule in the mass spectrum;

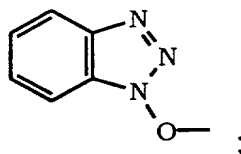
Bu-represents butyl;

Et-represents ethyl;

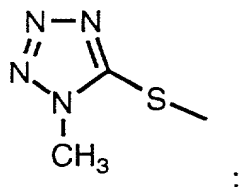
Me-represents methyl;

Ph-represents phenyl;

benzotriazol-1-yloxy represents



1-methyl-tetrazol-5-ylthio represents



alkyl-(including the alkyl portions of alkoxy, alkylamino and  
5 dialkylamino)-represents straight and branched carbon chains and  
contains from one to twenty carbon atoms, preferably one to six carbon  
atoms;

alkanediyl-represents a divalent, straight or branched  
hydrocarbon chain having from 1 to 20 carbon atoms, preferably 1 to 6  
10 carbon atoms, the two available bonds being from the same or different  
carbon atoms thereof, e.g., methylene, ethylene, ethylidene,  
-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>CHCH<sub>3</sub>-, -CHCH<sub>2</sub>CH<sub>3</sub>-, etc.

cycloalkyl-represents saturated carbocyclic rings branched or  
unbranched of from 3 to 20 carbon atoms, preferably 3 to 7 carbon atoms;

15 heterocycloalkyl-represents a saturated, branched or unbranched  
carbocyclic ring containing from 3 to 15 carbon atoms, preferably from 4 to  
6 carbon atoms, which carbocyclic ring is interrupted by 1 to 3 hetero  
groups selected from -O-, -S- or -NR<sup>10</sup>-(suitable heterocycloalkyl groups  
including 2- or 3-tetrahydrofuranyl, 2- or 3- tetrahydrothienyl, 2-, 3- or 4-  
20 piperidiny, 2- or 3-pyrrolidiny, 2- or 3-piperiziny, 2- or 4-dioxany, etc.);

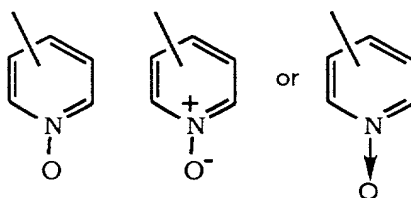
alkenyl-represents straight and branched carbon chains having at  
least one carbon to carbon double bond and containing from 2 to 12  
carbon atoms, preferably from 2 to 6 carbon atoms and most preferably  
from 3 to 6 carbon atoms;

25 alkynyl-represents straight and branched carbon chains having at  
least one carbon to carbon triple bond and containing from 2 to 12 carbon  
atoms, preferably from 2 to 6 carbon atoms;

aryl (including the aryl portion of aryloxy and aralkyl)-represents a  
carbocyclic group containing from 6 to 15 carbon atoms and having at  
30 least one aromatic ring (e.g., aryl is a phenyl ring), with all available  
substitutable carbon atoms of the carbocyclic group being intended as  
possible points of attachment, said carbocyclic group being optionally

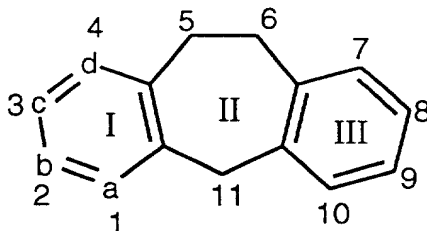
substituted (e.g., 1 to 3) with one or more of halo, alkyl, hydroxy, alkoxy, phenoxy, CF<sub>3</sub>, amino, alkylamino, dialkylamino, -COOR<sup>10</sup> or -NO<sub>2</sub>; and halo-represents fluoro, chloro, bromo and iodo; and

heteroaryl-represents cyclic groups, optionally substituted with R<sup>3</sup> and R<sup>4</sup>, having at least one heteroatom selected from O, S or N, said heteroatom interrupting a carbocyclic ring structure and having a sufficient number of delocalized pi electrons to provide aromatic character, with the aromatic heterocyclic groups preferably containing from 2 to 14 carbon atoms, e.g., triazolyl, 2-, 3- or 4-pyridyl or pyridyl N-oxide (optionally substituted with R<sup>3</sup> and R<sup>4</sup>), wherein pyridyl N-oxide can be represented as:



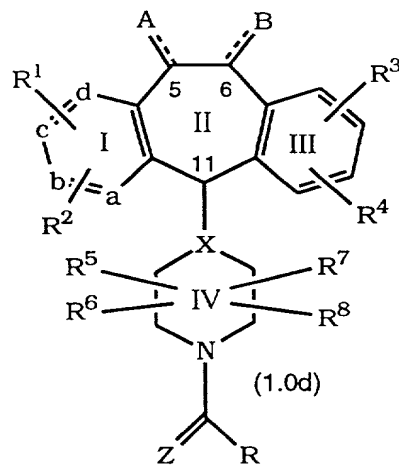
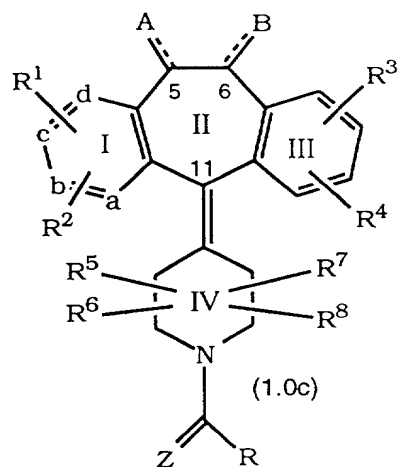
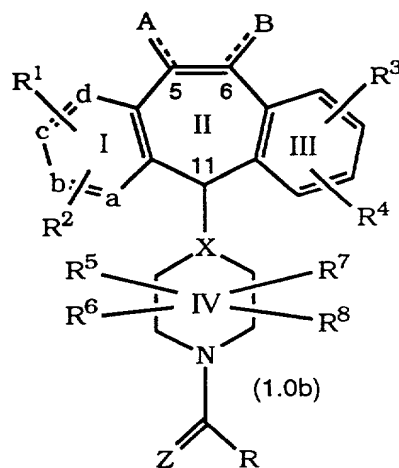
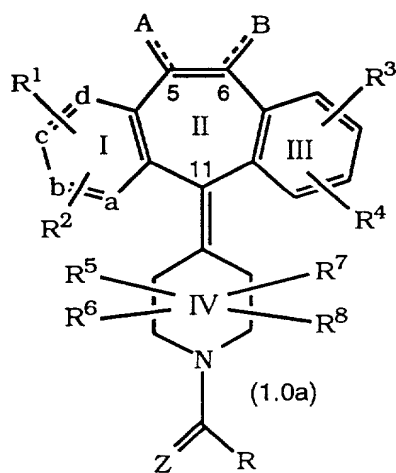
The following solvents and reagents are referred to herein by the abbreviations indicated: tetrahydrofuran (THF); ethanol (EtOH); methanol (MeOH); acetic acid (HOAc or AcOH); ethyl acetate (EtOAc); N,N-dimethylformamide (DMF); trifluoroacetic acid (TFA); trifluoroacetic anhydride (TFAA); 1-hydroxybenzotriazole (HOBt); m-chloroperbenzoic acid (MCPBA); triethylamine (Et<sub>3</sub>N); diethyl ether (Et<sub>2</sub>O); ethyl chloroformate (ClCO<sub>2</sub>Et); 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (DEC)

Reference to the position of the substituents R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, and R<sup>4</sup> is based on the numbered ring structure:



For example, R<sup>1</sup> can be at the C-4 position and R<sup>2</sup> can be at the C-2 or C-3 position. Also, for example, R<sup>3</sup> can be at the C-8 position and R<sup>4</sup> can be at the C-9 position.

Representative structures of Formula 1.0 include but are not limited to:



and

Preferably, for the compounds of Formula 1.0 (including 1.0a to 1.0d):

- 5 each of a, b, c, and d are C (carbon); or  
one of a, b, c and d (most preferably a) represents N or NO, most preferably N, and the remaining a, b, c and d groups represent CR<sup>1</sup> or CR<sup>2</sup>;
- 10 each R<sup>1</sup> and each R<sup>2</sup> is independently selected from H, halo (e.g., Cl, Br and F), -CF<sub>3</sub>, -OR<sup>10</sup> (e.g., hydroxy and alkoxy (e.g., -OCH<sub>3</sub>)), alkyl (e.g., methyl and t-butyl, said alkyl group being optionally substituted with halo), benzotriazol-1-yloxy, -S(O)<sub>t</sub>R<sup>11</sup> (e.g., -SCH<sub>2</sub>CH<sub>3</sub>), -SR<sup>11</sup>C(O)OR<sup>11</sup> (e.g., -SCH<sub>2</sub>CO<sub>2</sub>CH<sub>3</sub>), -SR<sup>10</sup> (e.g., R<sup>10</sup> represents -CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>) and 1-methyl-tetrazol-5-ylthio; most preferably R<sup>1</sup> and R<sup>2</sup> are independently H,
- 15 halo, -CF<sub>3</sub>, lower alkyl (e.g., C<sub>1</sub> to C<sub>4</sub>, more preferably methyl) or benzotriazol-1-yloxy; more preferably R<sup>1</sup> is Cl or H, and R<sup>2</sup> is H, Cl or Br; still more preferably R<sup>1</sup> is at the C-4 position, and R<sup>2</sup> is at the C-3 position; even more preferably R<sup>2</sup> is Br, Cl or I;

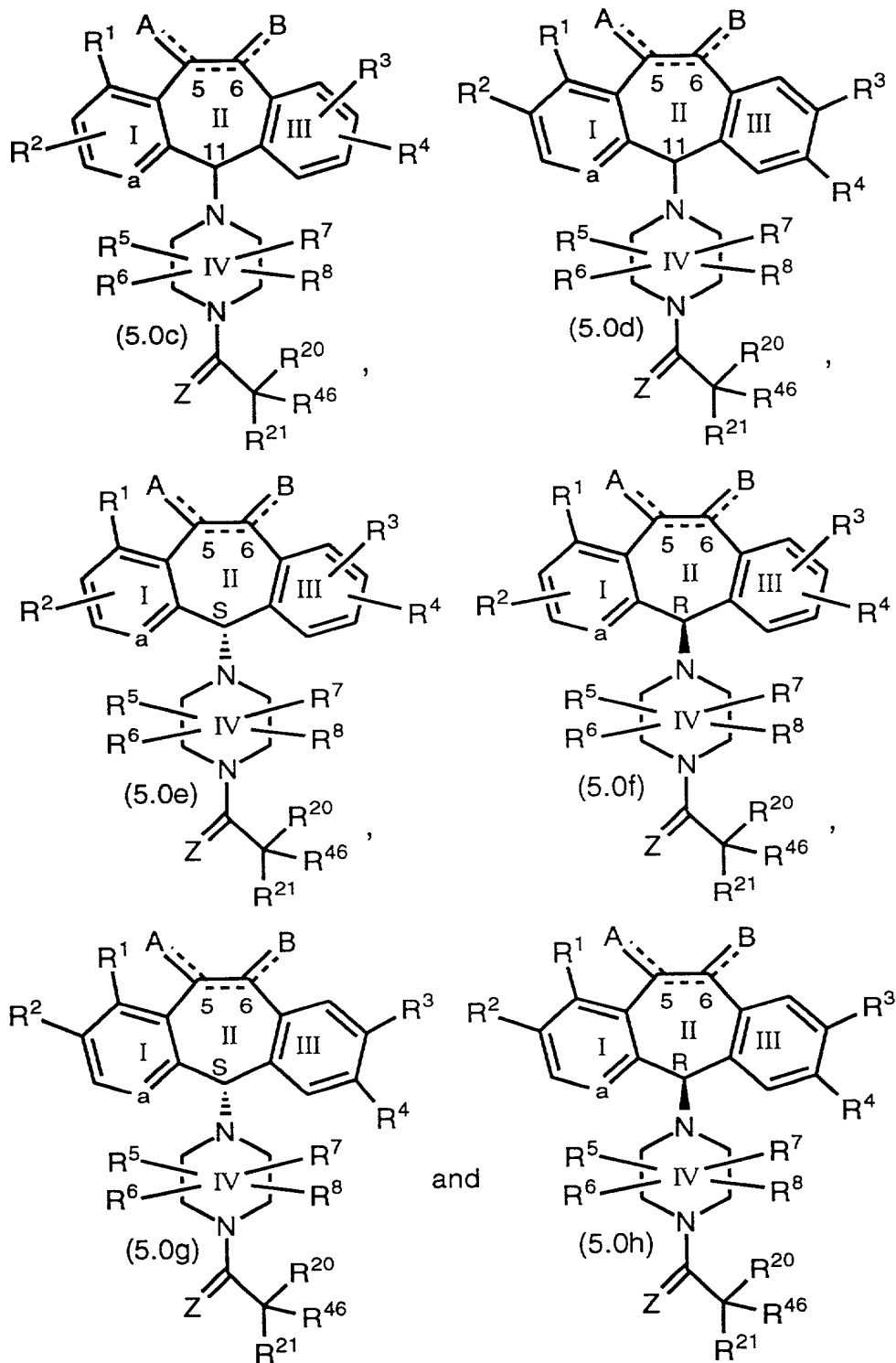
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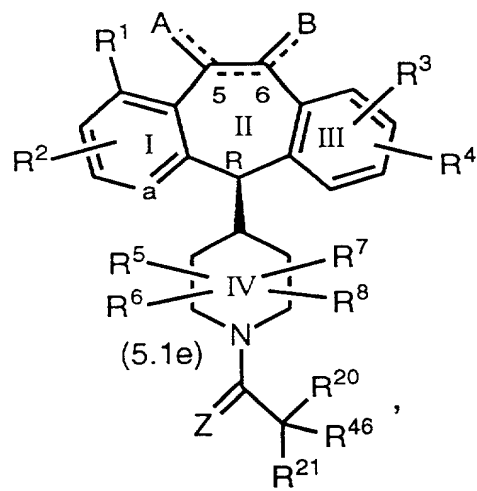
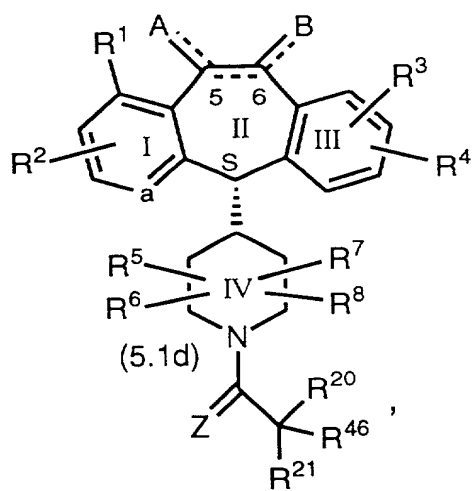
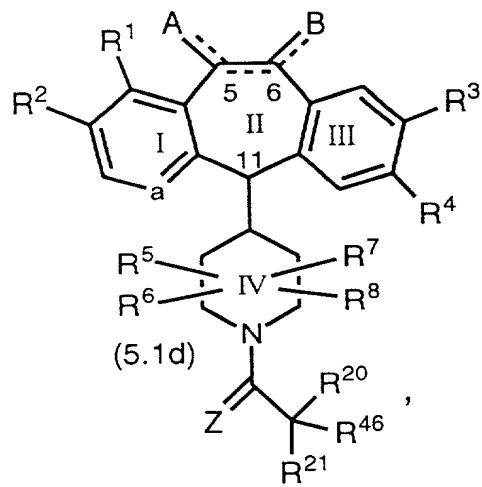
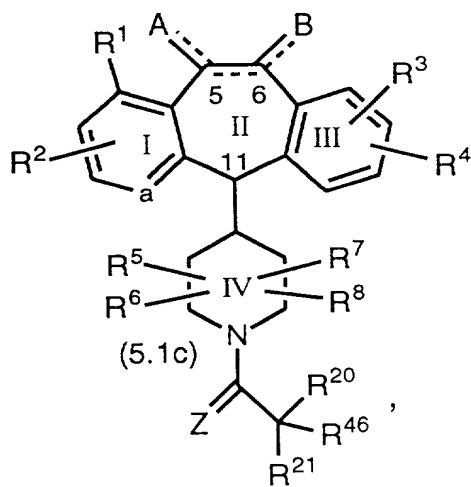
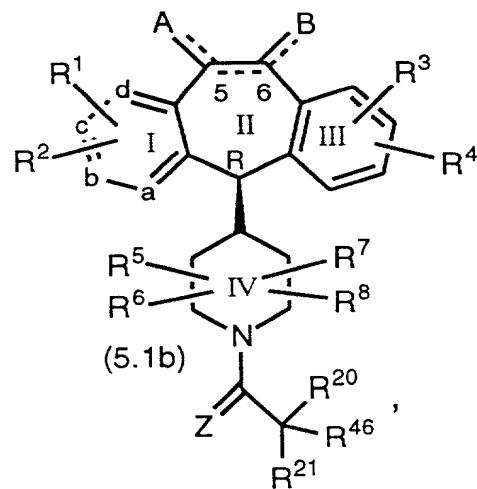
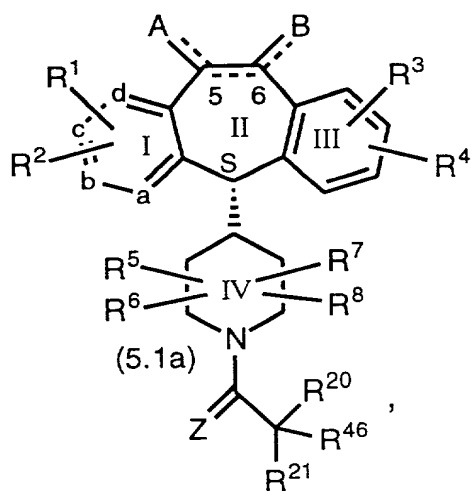
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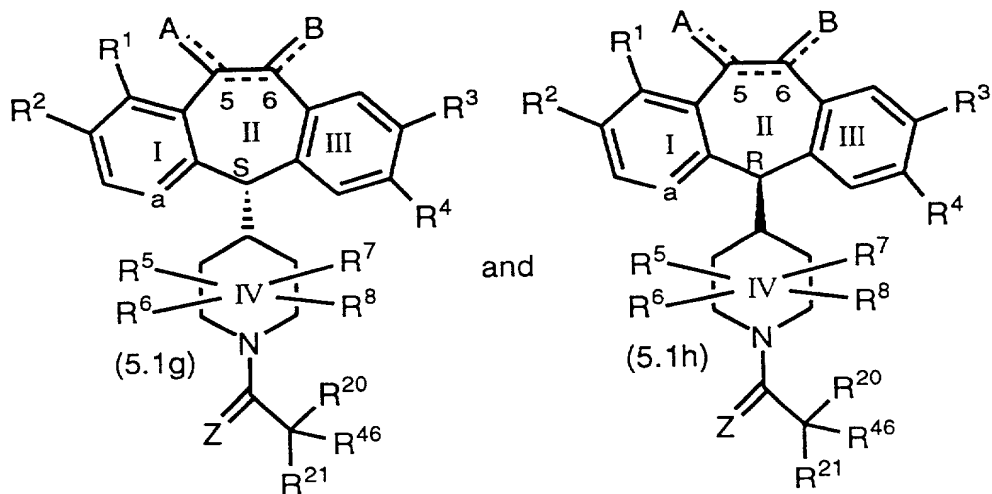
Z represents O or S, and most preferably O.

25

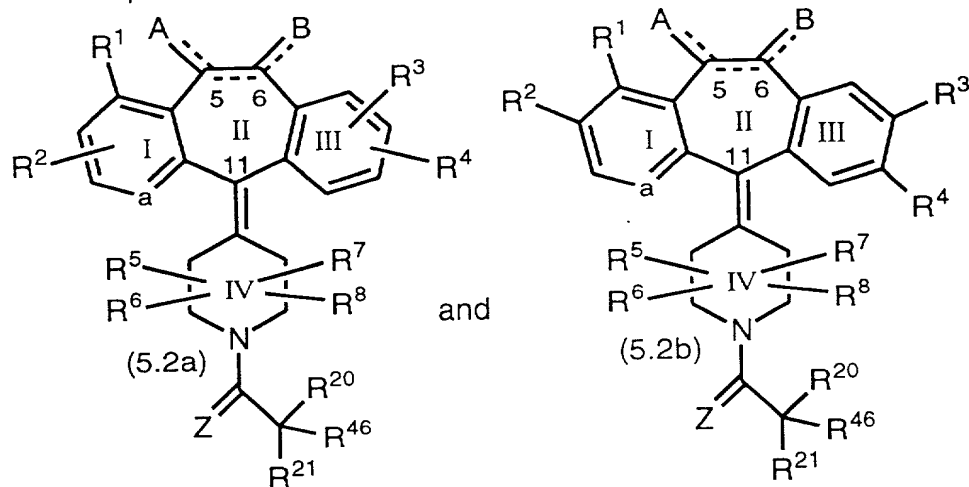


Compounds of Formula 5.1 include:

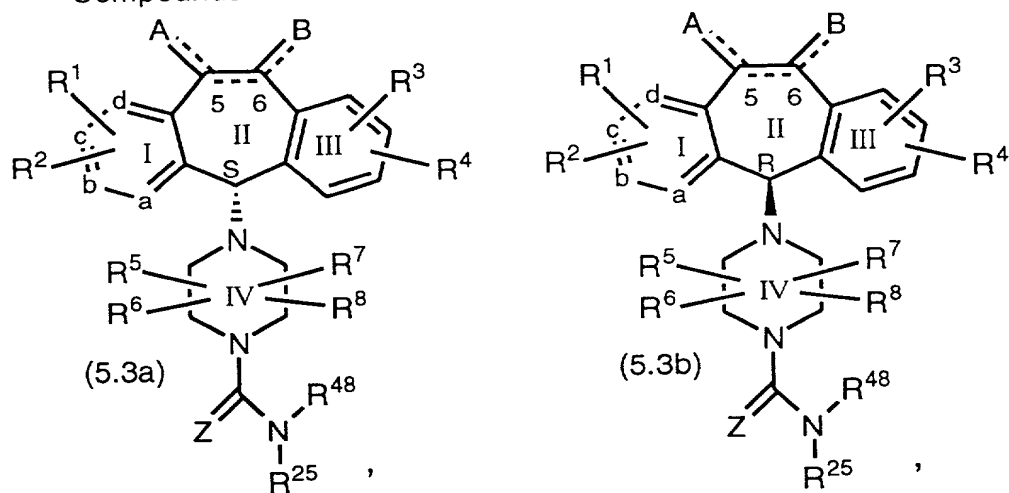




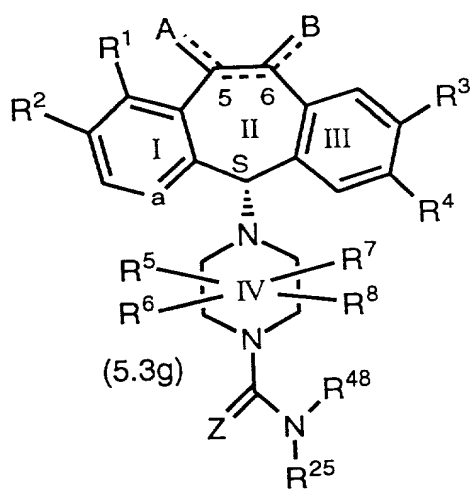
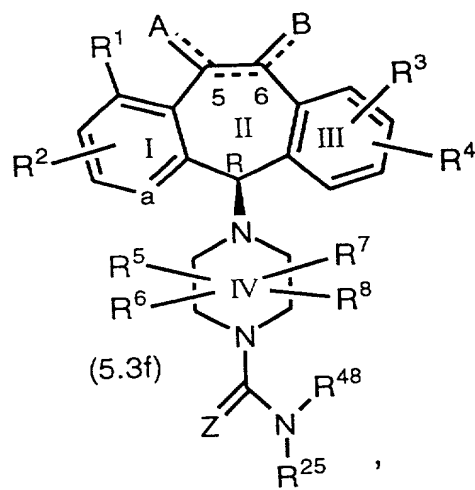
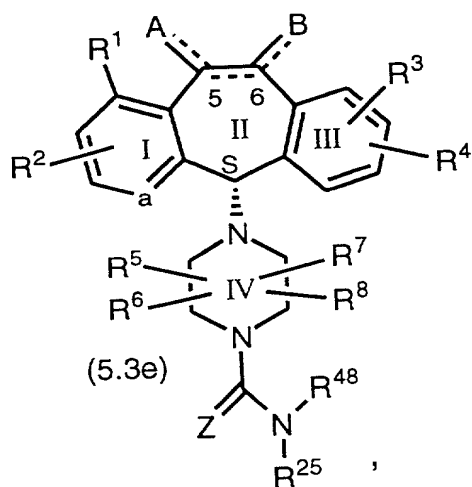
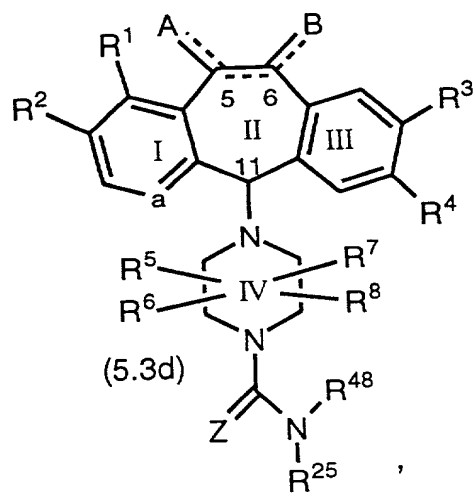
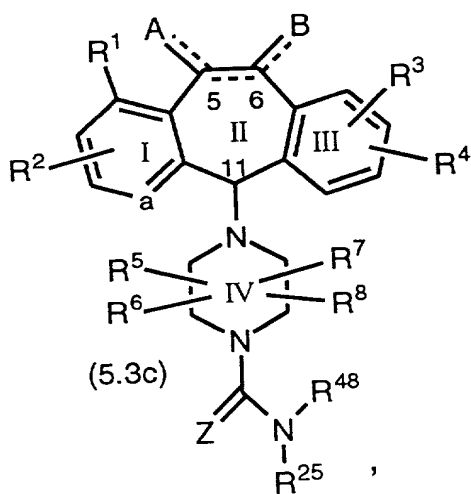
Compounds of Formula 5.2 additionally include:



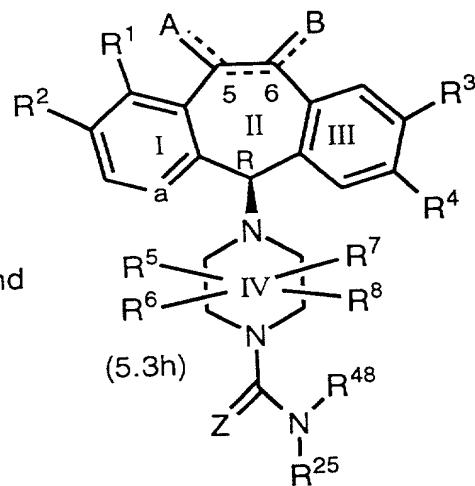
Compounds of Formula 5.3 include:



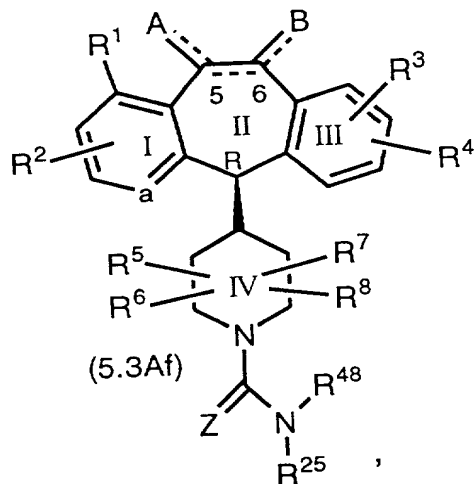
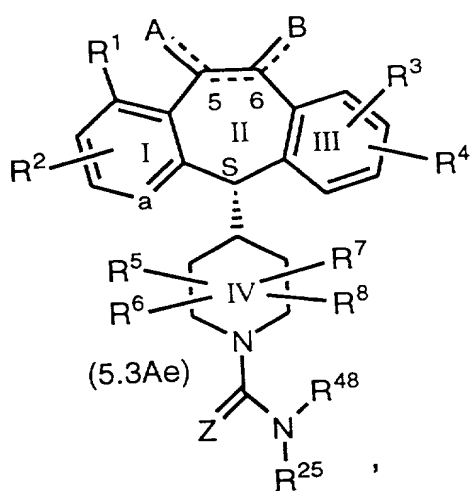
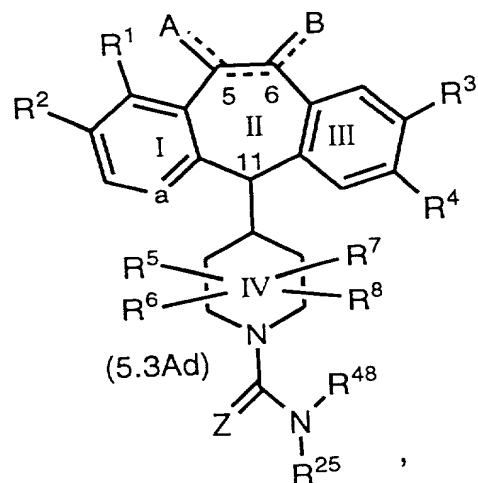
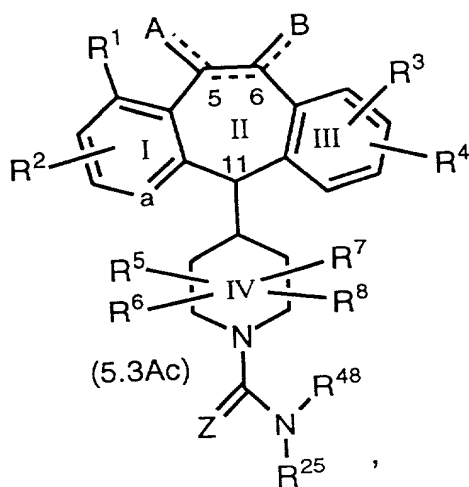
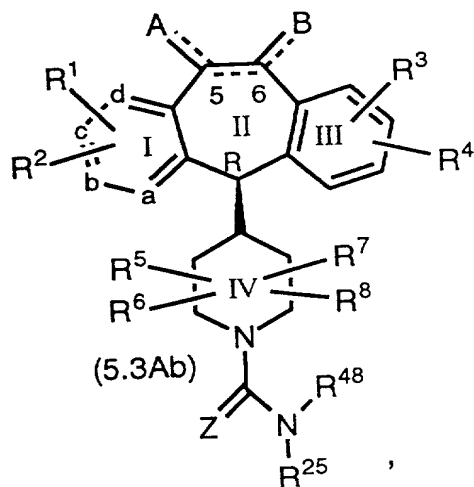
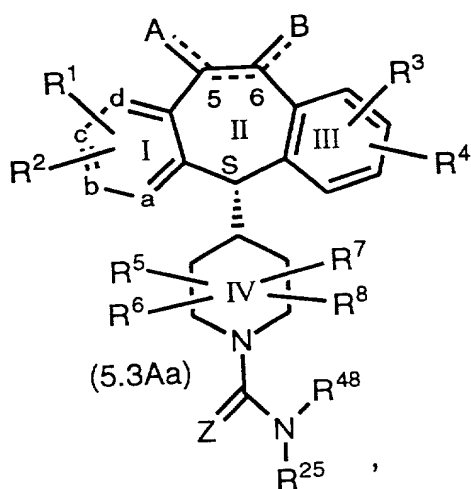


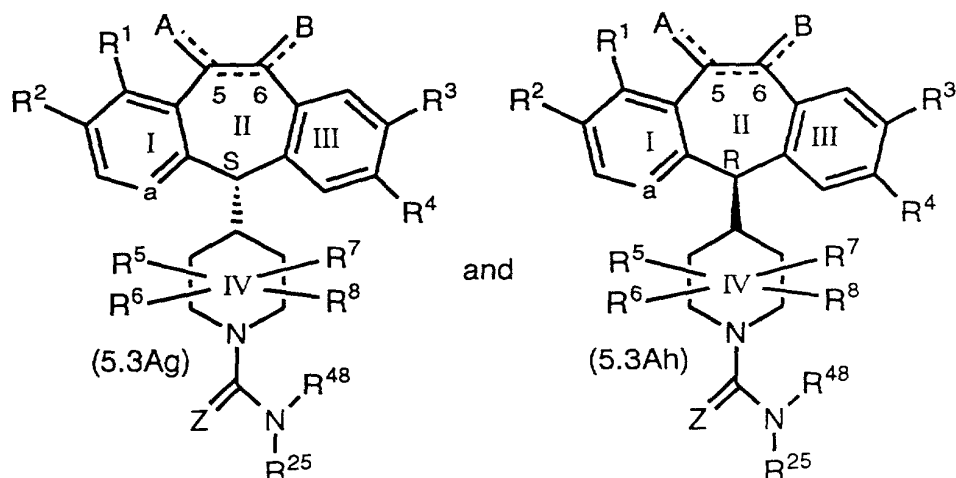


and



Compounds of formula 5.3A include:



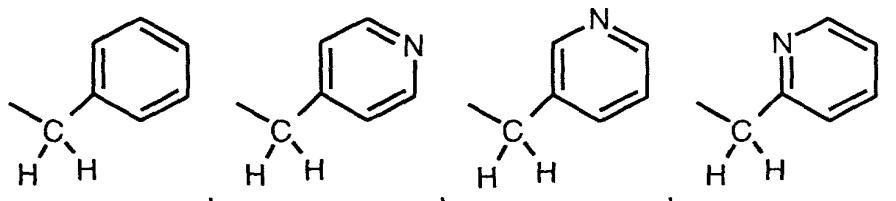


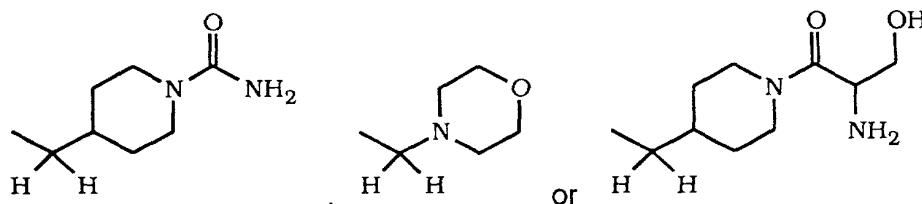
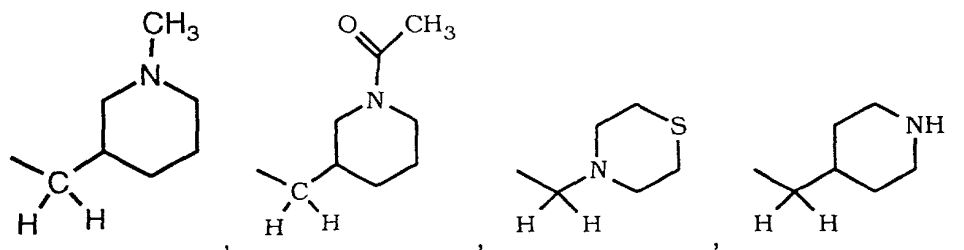
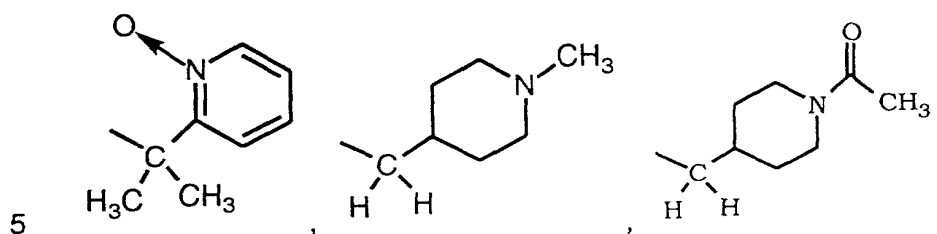
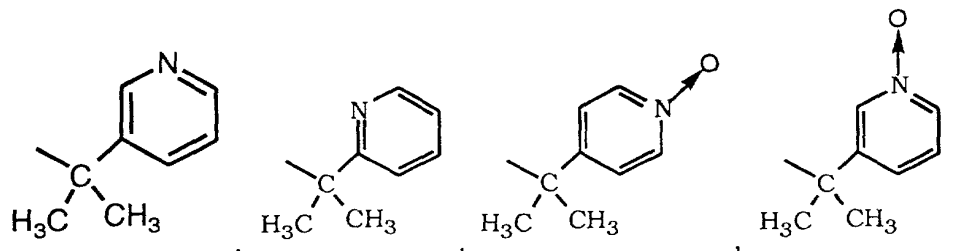
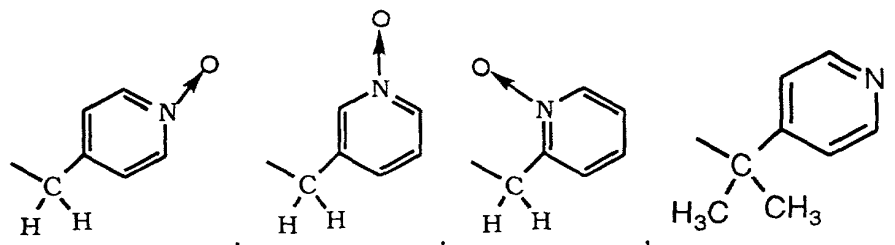
For the compounds of Formulas 5.0, 5.0a-5.0g, 5.1, 5.1a-5.1g, 5.2, 5.2a-5.2b, 5.3, 5.3a-5.3g, 5.3A, 5.3Aa-5.3Ag, and 5.3B, the definitions of the substituents are as defined for Formula 1.0.

- 5                      Preferably, for compounds of Formulas 5.0, 5.0a-5.0g, 5.1, 5.1a-5.1g, 5.2, and 5.2a-5.2b,  $R^{46}$  is selected from piperidine Ring V, heteroaryl, phenyl, substituted phenyl, substituted pyridyl or substituted pyridyl N-oxide, and  $R^{20}$  and  $R^{21}$  are independently selected from H or alkyl. Most preferably,  $R^{46}$  is pyridyl, pyridyl N-oxide or piperidine Ring V.
- 10                    More preferably,  $R^{46}$  is pyridyl, pyridyl N-oxide or piperidine Ring V and both  $R^{20}$  and  $R^{21}$  are hydrogen or both  $R^{20}$  and  $R^{21}$  are alkyl (still more preferably methyl).

- 15                    Even more preferably,  $R^{46}$  is selected from 3-pyridyl, 4-pyridyl, 3-pyridyl N-oxide, 4-pyridyl N-oxide, 4-N-methylpiperidinyl, 3-N-methylpiperidinyl, 4-N-acetylpiperidinyl or 3-N-acetylpiperidinyl, and both  $R^{20}$  and  $R^{21}$  are hydrogen or both  $R^{20}$  and  $R^{21}$  are alkyl (still even more preferably methyl). Even still more preferably,  $R^{46}$  is selected from 3-pyridyl, 3-pyridyl N-oxide, 4-pyridyl, and 4-pyridyl N-oxide, and both  $R^{20}$  and  $R^{21}$  are hydrogen or both  $R^{20}$  and  $R^{21}$  are methyl.

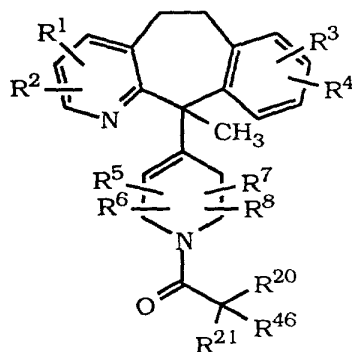
- 20                    Examples of the  $R^{42}$  groups include:



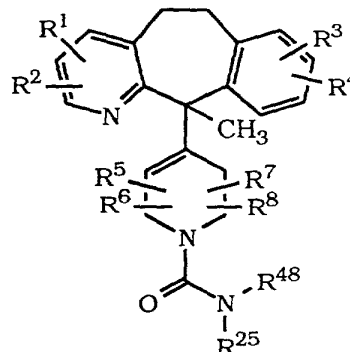


10 Preferably for the compounds of Formulas 5.3, 5.3a-5.3g, 5.3A, 5.3Aa-5.3Ag, and 5.3B, R<sup>25</sup> represents phenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, or 2-, 3- or 4-pyridyl N-oxide, and most preferably 4-pyridyl or 4-pyridyl N-oxide. More preferably, R<sup>48</sup> represents H or methyl and still more preferably H.

15 Compounds of the formula 7.0c include compounds of the formula:



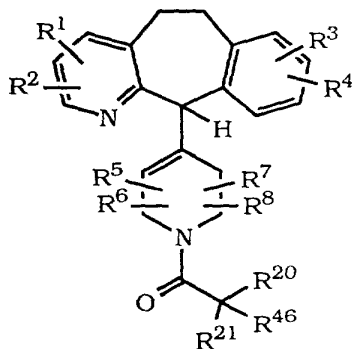
(7.0e) and



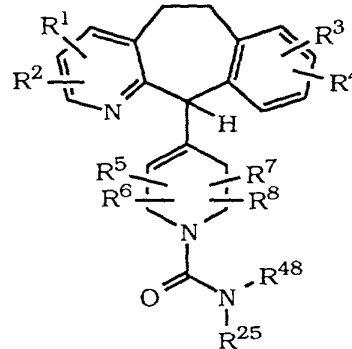
(7.0f).

wherein R<sup>21</sup>, R<sup>20</sup>, R<sup>46</sup>, R<sup>25</sup> and R<sup>48</sup> are as defined above for compounds of the formula 1.0.

Compounds of the formula 7.0b include compounds of the formula:



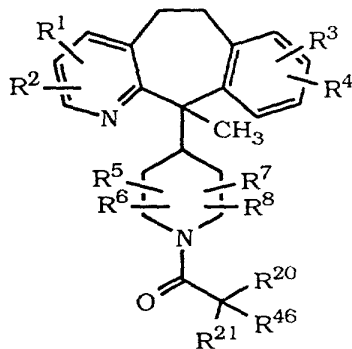
(7.0g) and



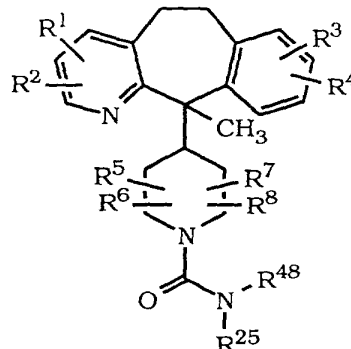
(7.0h).

wherein R<sup>21</sup>, R<sup>20</sup>, R<sup>46</sup>, R<sup>25</sup> and R<sup>48</sup> are as defined above for compounds of the formula 1.0.

Compounds of the formula 7.0a include compounds of the formula:



(7.0j) and



(7.0k).

wherein R<sup>21</sup>, R<sup>20</sup>, R<sup>46</sup>, R<sup>25</sup> and R<sup>48</sup> are as defined above for compounds of the formula 1.0.

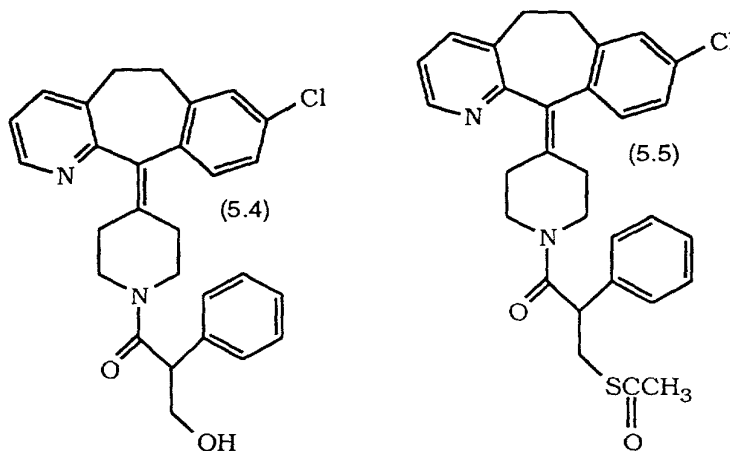
Preferably for compounds of the formula 7.0e, 7.0g and 7.0j the group R<sup>46</sup> is selected from piperidine ring V, heteroaryl, phenyl, substituted phenyl, substituted pyridyl or substituted pyridyl N-oxide, and

$R^{20}$  and  $R^{21}$  are independently selected from H or alkyl. Most preferably R is pyridyl, pyridyl N-oxide or piperidine ring V. It is also preferred that  $R^{20}$  and  $R^{21}$  are both H or are both alkyl, preferably methyl.

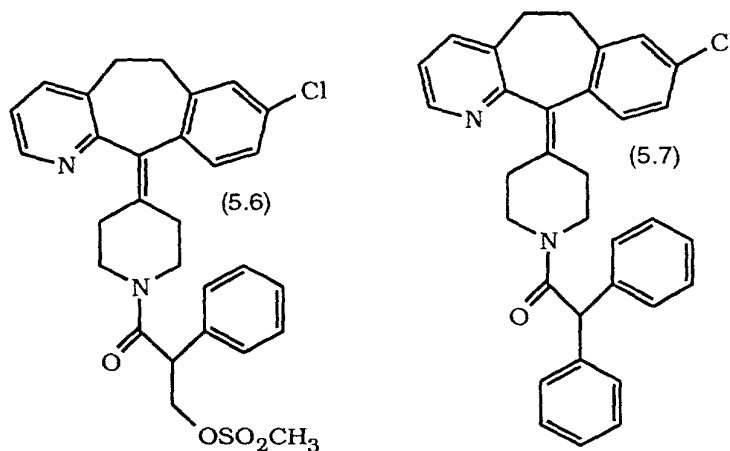
5 Preferably for compounds of the formula 7.0f, 7.0h and 7.0k, the group  $R^{25}$  is phenyl, 3-pyridyl, 4-pyridyl, 3-pyridyl N-oxide, 4-pyridyl N-oxide or piperidine ring V. More preferably  $R^{48}$  is H or methyl, with H being most preferred.

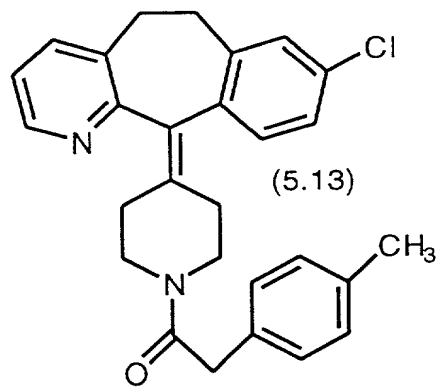
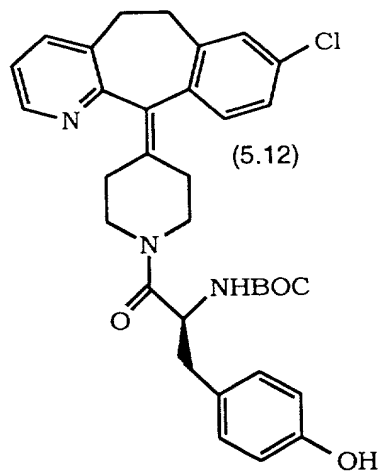
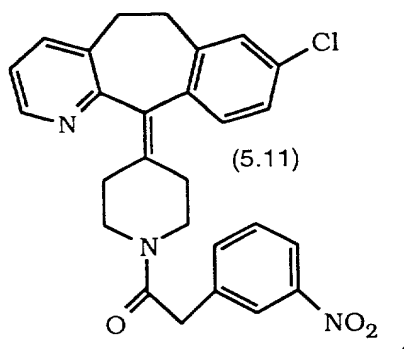
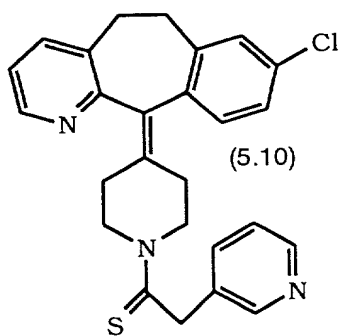
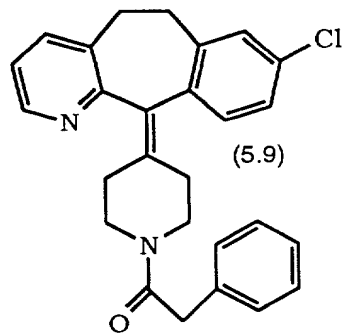
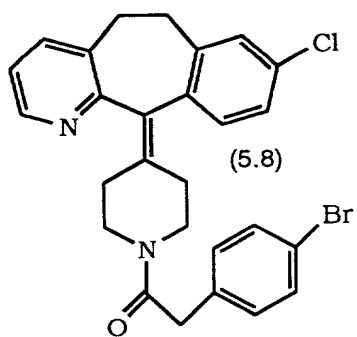
10 Preferably for the compounds of formula 7.0a, 7.0b, 7.0c, 7.0e, 7.0f, 7.0g, 7.0h, 7.0j and 7.0k the groups  $R^5$ ,  $R^6$ ,  $R^7$  and  $R^8$  are H, and  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^4$  are independently selected from H, halo,  $-NO_2$ ,  $-N(R^{10})_2$ , alkyl, alkenyl, alkynyl,  $-COR^{10}$ ,  $-CO_2R^{10}$ ,  $-CF_3$ ,  $-OR^{10}$ , and  $-CN$ , wherein  $R^{10}$  is as defined above for compounds of the formula 1.0.

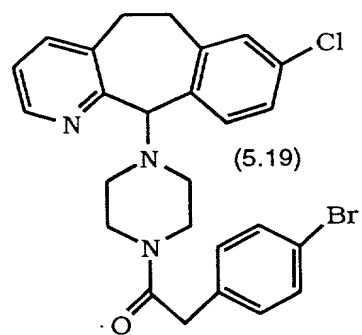
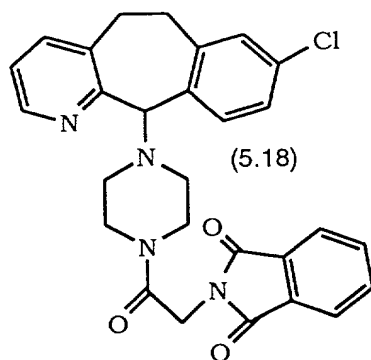
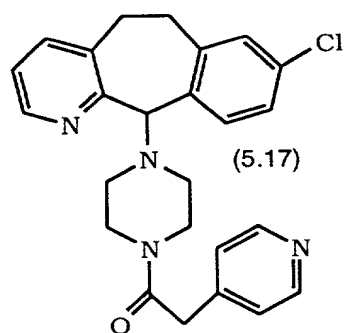
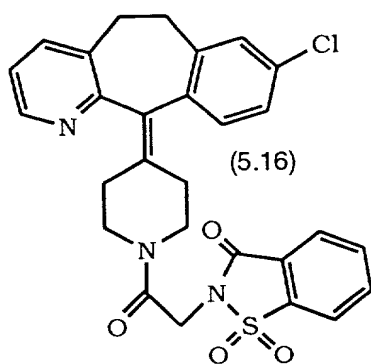
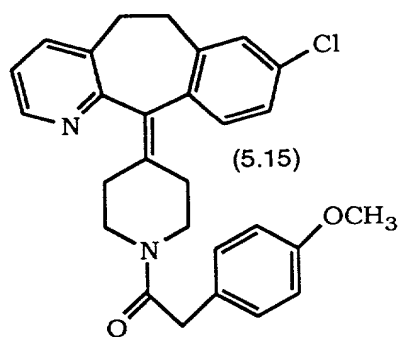
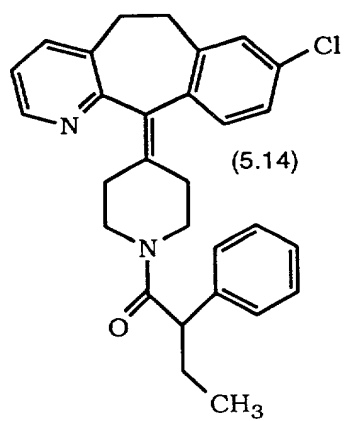
Representative compounds of the invention include:



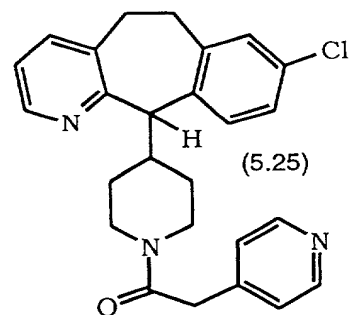
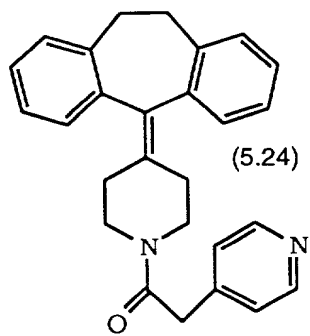
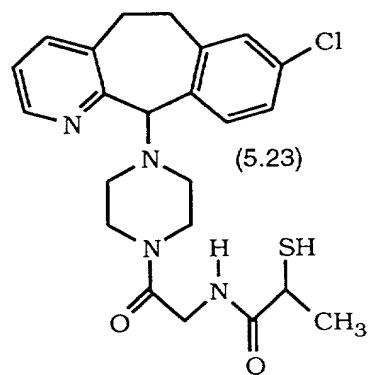
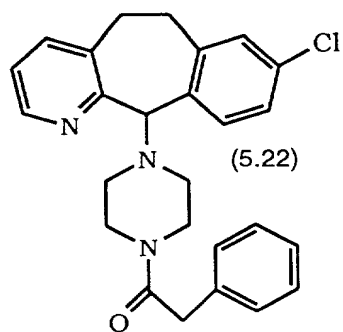
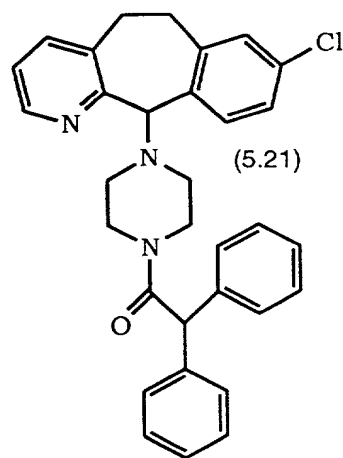
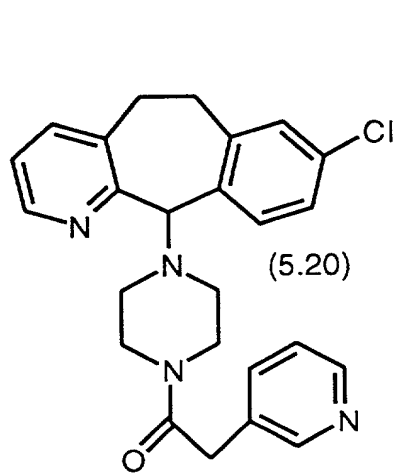
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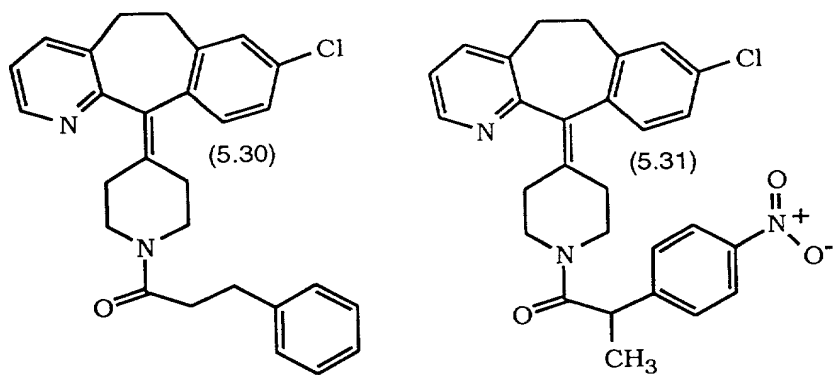
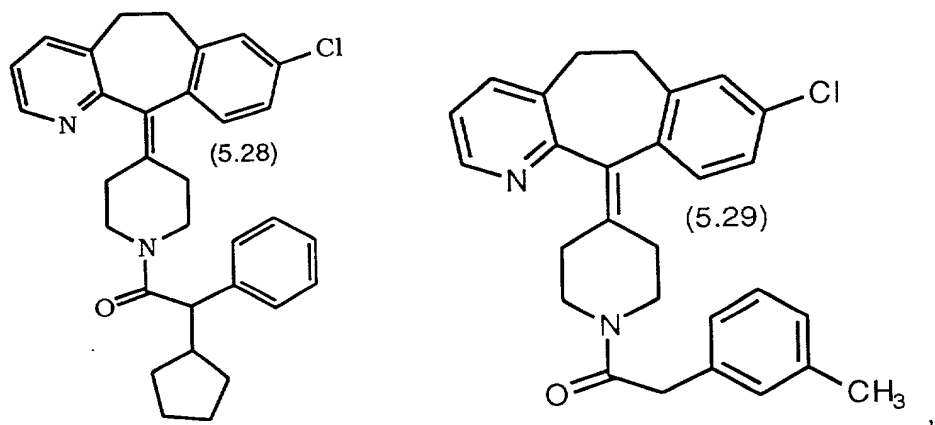
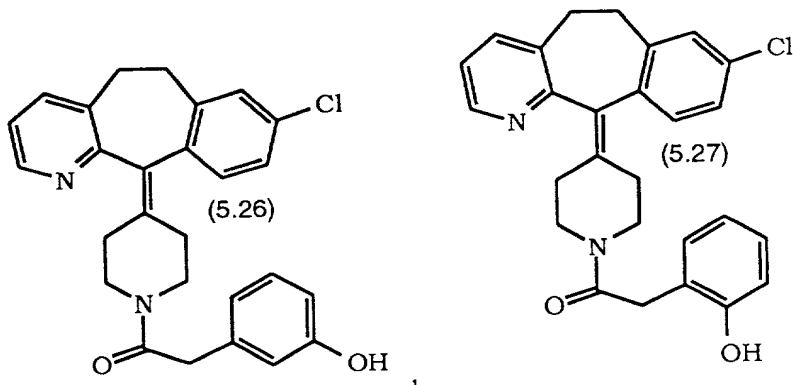


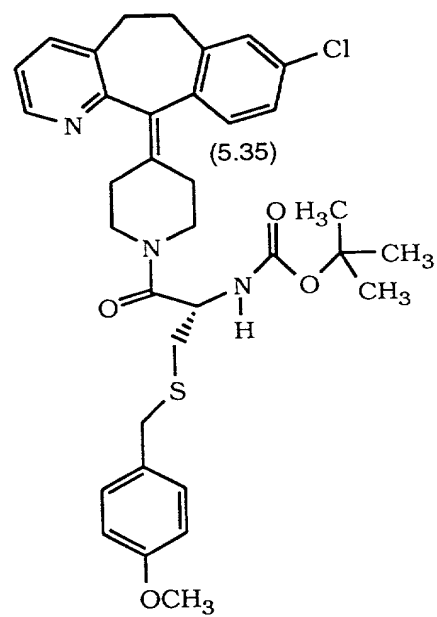
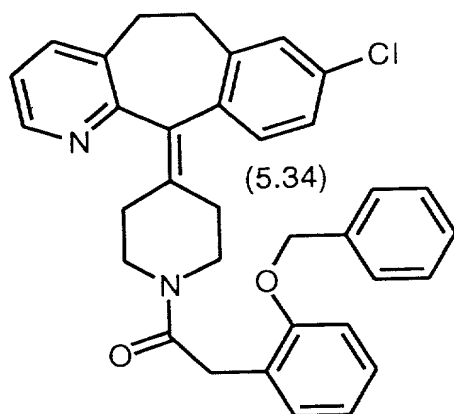
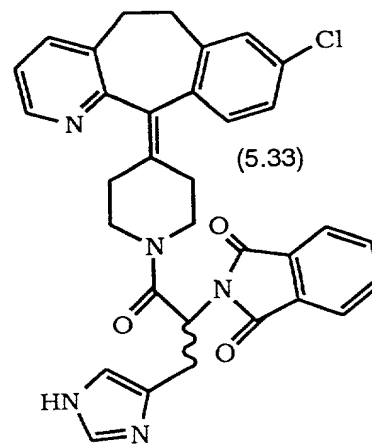
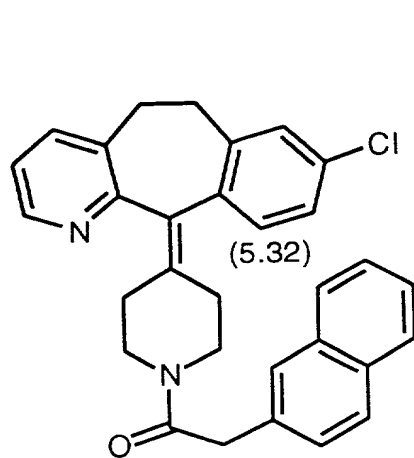


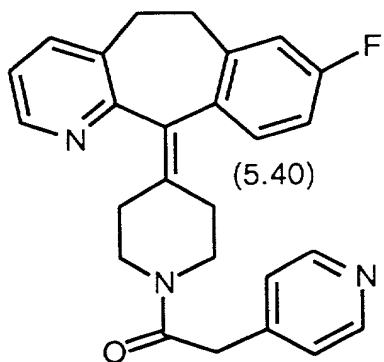
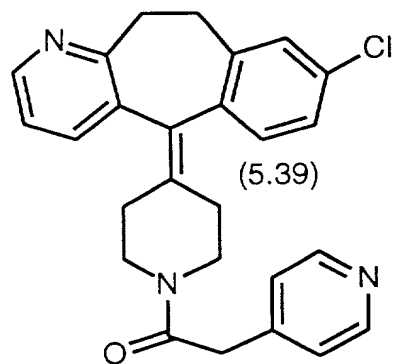
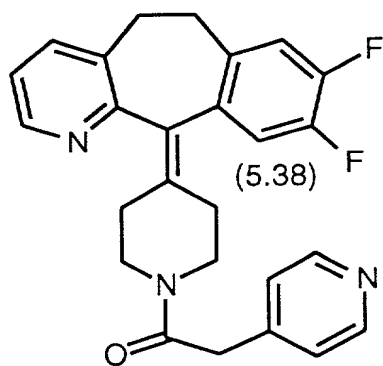
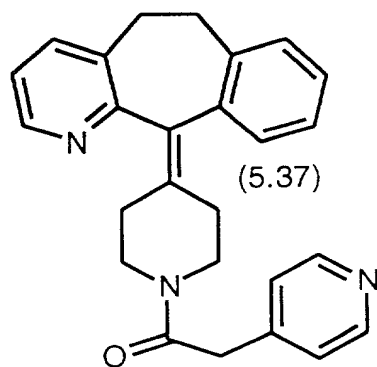
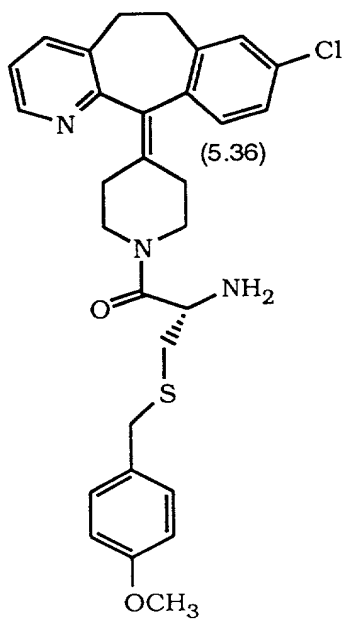


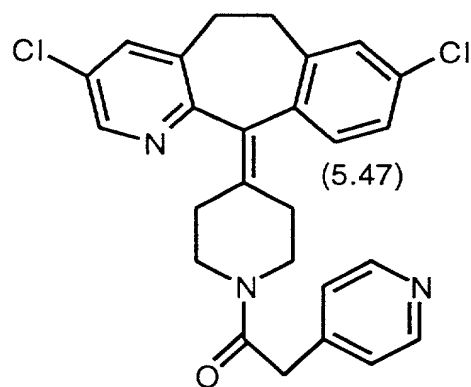
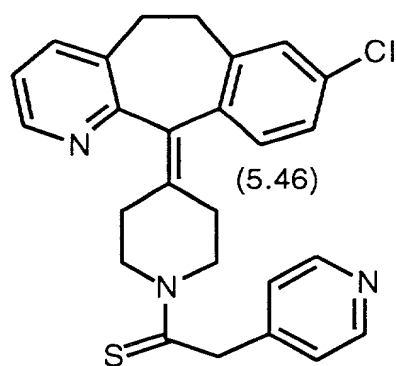
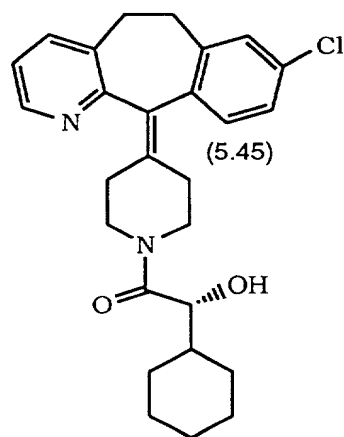
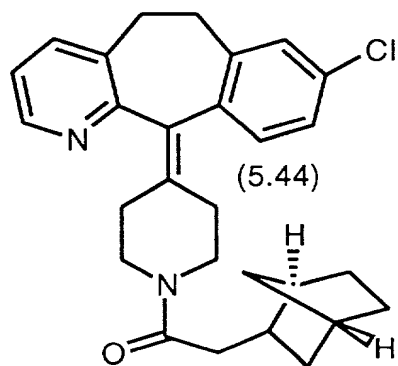
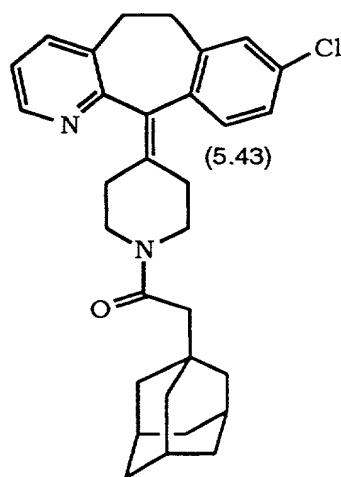
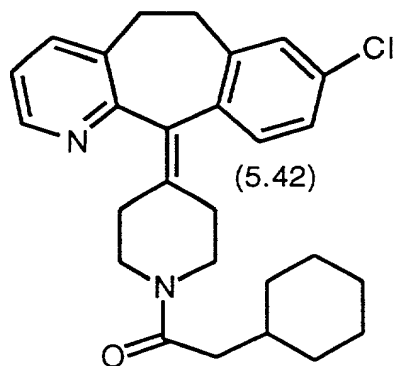


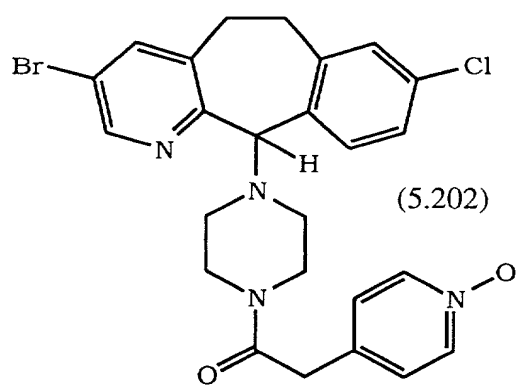
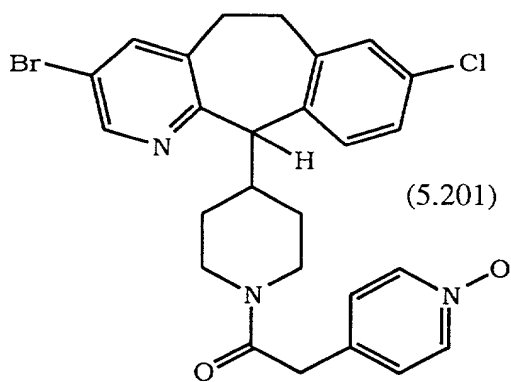
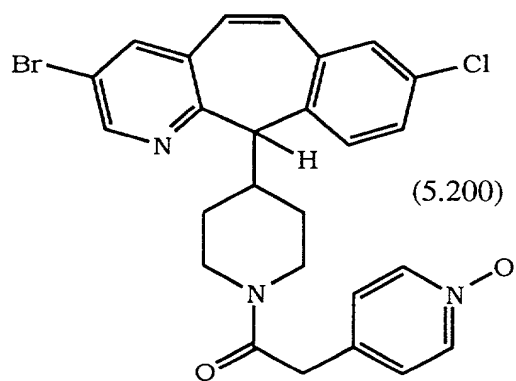
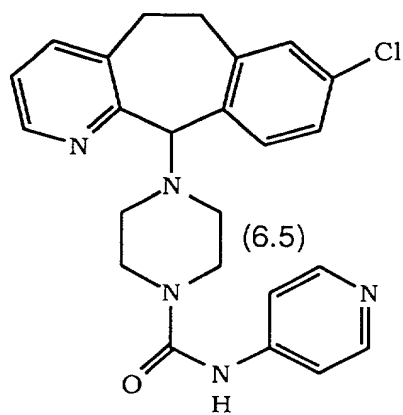
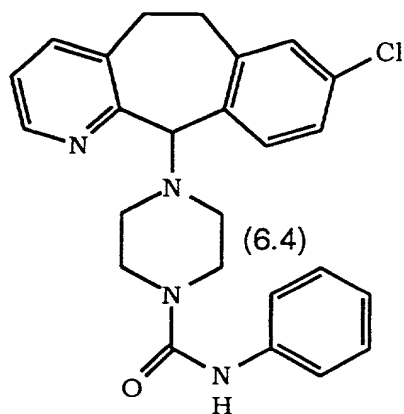
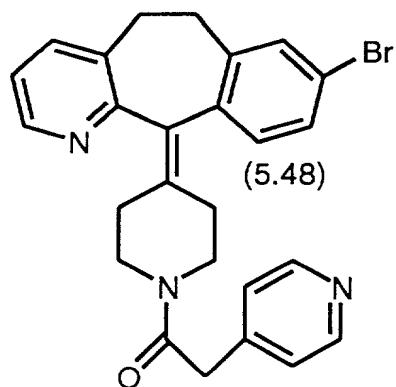


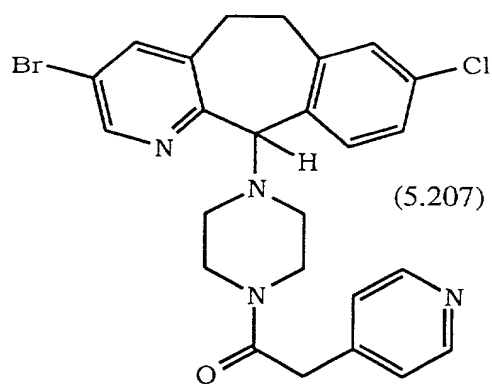
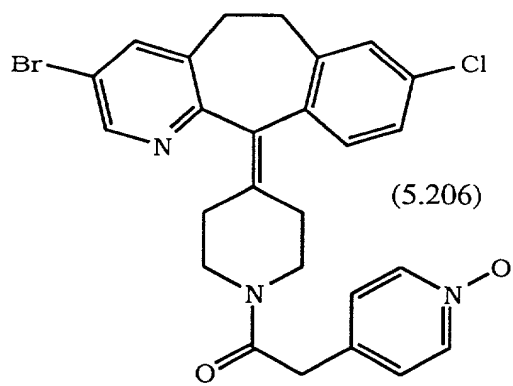
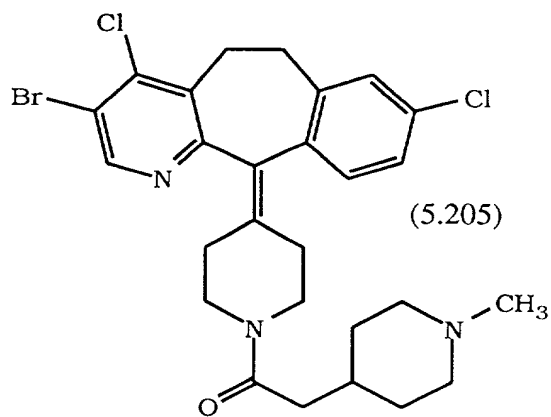
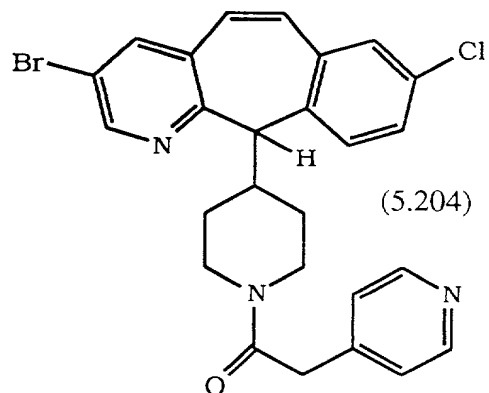
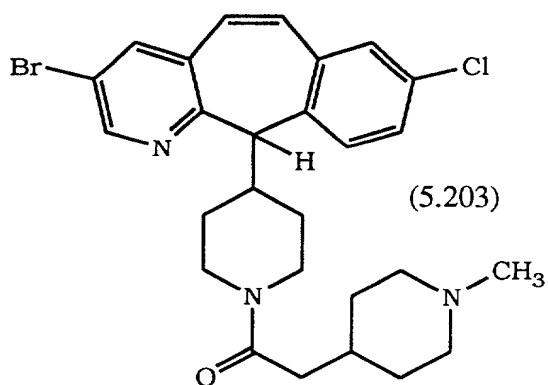


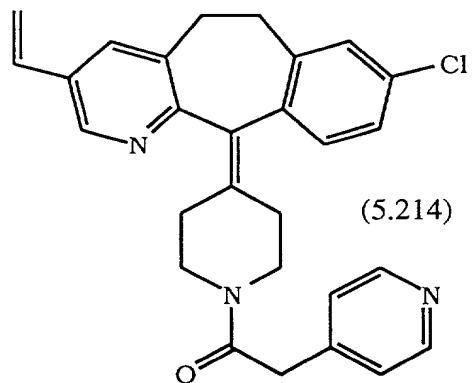
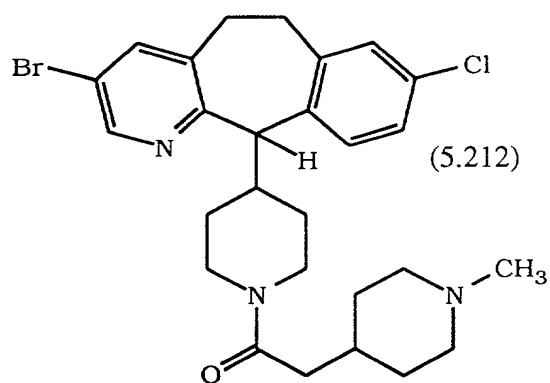
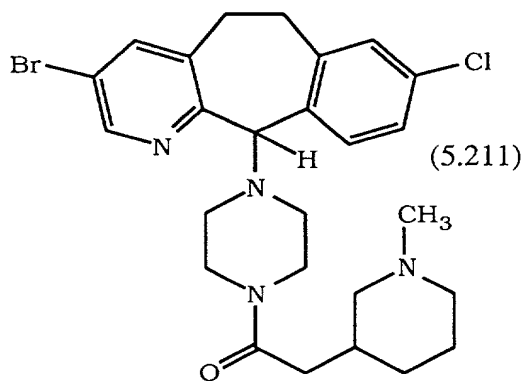
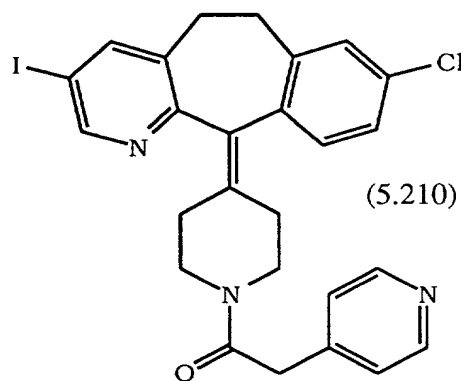
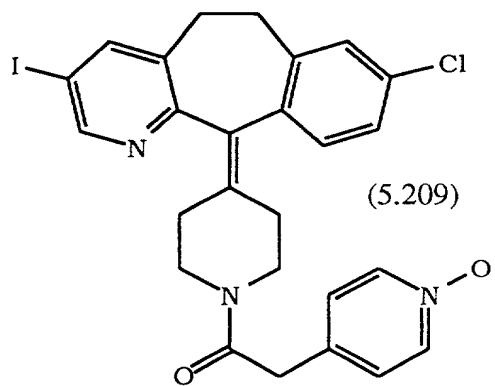
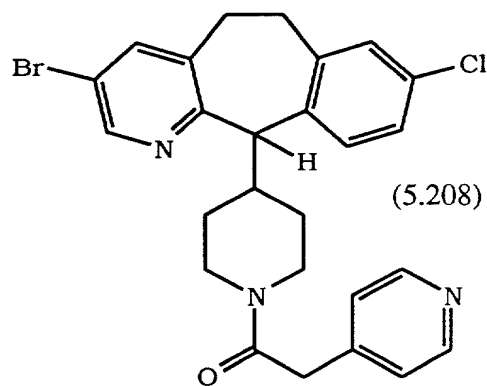




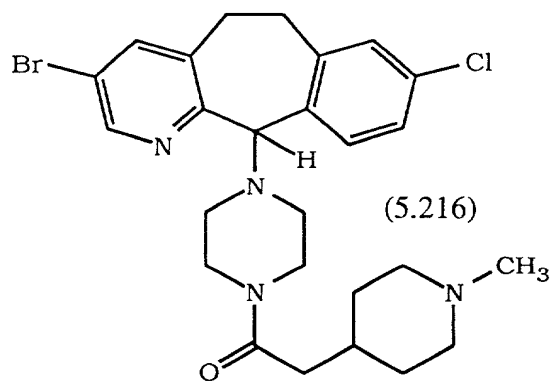
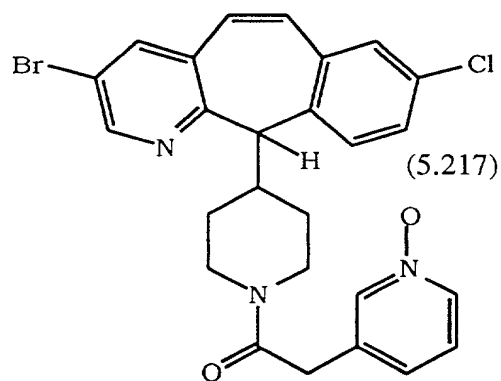
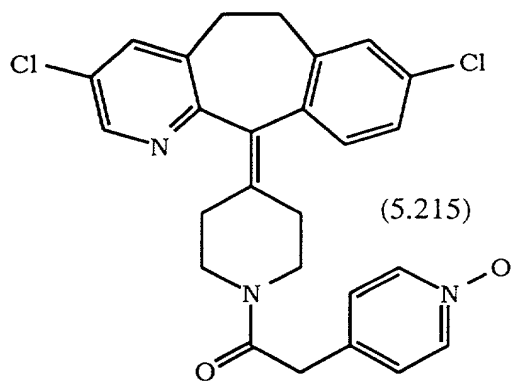
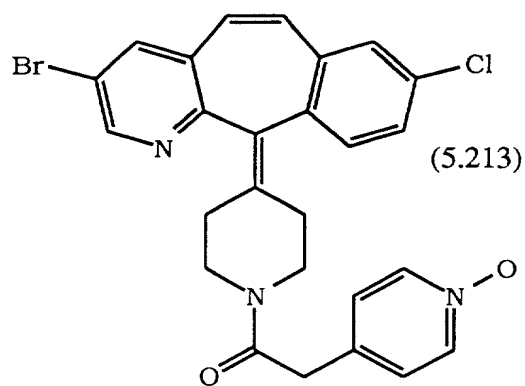


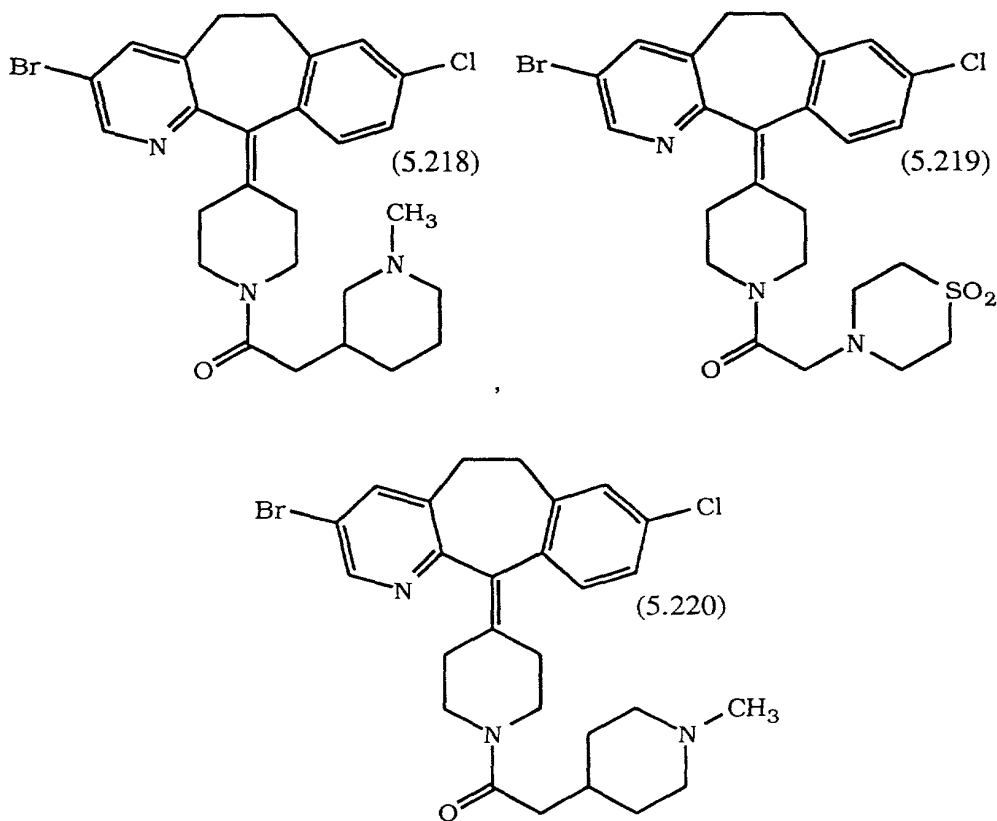












5 Preferred compounds of this invention are selected from the group consisting of compounds of Examples: 1, 2, 3, 4, 5, 6, 19, 42, 43, 44, 45, 46, 47, 48, 49, 75, 76, 78, 82, 83, 84, 85, 89, 121, 180, 182, 183, 184, 187 (6.7 and 6.8), 192, 196, 197, 198, 200, 201, 206, 222, 223, 224, 225, 226, 227, 233, 234, 236, 239, 246, 247, 248, 249, 250, 251, 261, 262, 266, 267, 10 269, 273, 276, 283, 285, 286, 287, 288, 289, 291, 292, 293, 299, 300, 301, 303, 307, 309, 311, 312, 313, 314, 316, 350, 351, 352, 354 and 356.

More preferred compounds of this invention are selected from the group consisting of compounds of Examples: 1, 2, 42, 43, 75, 78, 82, 180, 183, 187 (6.7 and 6.8), 196, 197, 198, 200, 222, 223, 224, 227, 233, 234, 15 246, 247, 248, 249, 250, 251, 266, 269, 273, 283, 285, 286, 291, 292, 300, 301, 303, 307, 311, 312, 313, 314, 350, 351, 352, 354 and 356.

Even more preferred compounds of this invention are selected from the group consisting of compounds of Examples: 82, 197, 233, 246, 266, 312, 351, 352, 354 and 356.

20 Also more preferred are the compounds of Examples: 426, 400-G, 400-C, 400-F, 400-E, 425-H, 401, 400-B, 400, 400-L, 425-U, 413, 400-J, 417-B, 438, 411-W, 425-O, 400-D, 400-K, 410-G and 400-H.

Lines drawn into the ring systems indicate that the indicated bond may be attached to any of the substitutable ring carbon atoms.

Certain compounds of the invention may exist in different isomeric (e.g., enantiomers and diastereoisomers) forms. The invention  
5 contemplates all such isomers both in pure form and in admixture, including racemic mixtures. Enol forms are also included.

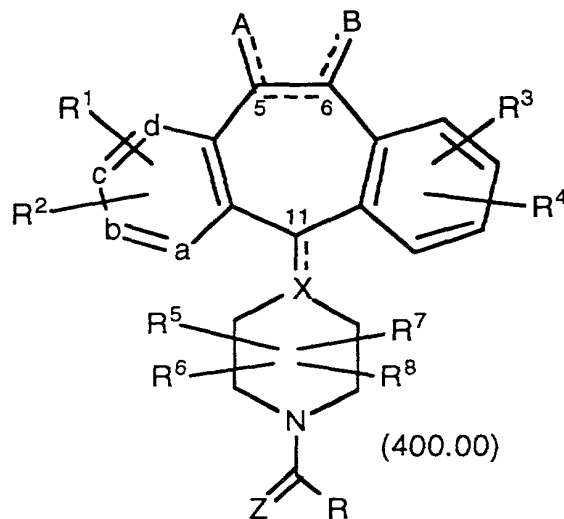
Certain tricyclic compounds will be acidic in nature, e.g. those compounds which possess a carboxyl or phenolic hydroxyl group. These compounds may form pharmaceutically acceptable salts. Examples of  
10 such salts may include sodium, potassium, calcium, aluminum, gold and silver salts. Also contemplated are salts formed with pharmaceutically acceptable amines such as ammonia, alkyl amines, hydroxyalkylamines, N-methylglucamine and the like.

Certain basic tricyclic compounds also form pharmaceutically  
15 acceptable salts, e.g., acid addition salts. For example, the pyrido-nitrogen atoms may form salts with strong acid, while compounds having basic substituents such as amino groups also form salts with weaker acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric,  
20 succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those in the art. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt in the conventional manner. The free base forms may be regenerated by treating the salt with a suitable dilute aqueous base  
25 solution such as dilute aqueous NaOH, potassium carbonate, ammonia and sodium bicarbonate. The free base forms differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the acid and base salts are otherwise equivalent to their respective free base forms for purposes of the invention.

30 All such acid and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

Compounds of Formula 1.0 wherein R is  $-N(R^{10})_2$ , and compounds  
35 of Formulas 5.3, 5.3A and 5.3B can be prepared by reacting compound 405.00 (described below) with an isocyanate ( $R^{10}-N=C=O$ ) in a solvent such as DMF,  $CH_2Cl_2$  or THF in accordance with methods known in the art.

The following processes may be employed to produce compounds of the invention--i.e., compounds of Formula 1.0 represented by compounds of Formulas 5.0, 5.1, 5.2 and 5.3. For purposes of describing the processes, the compounds are represented by Formula 400.00:

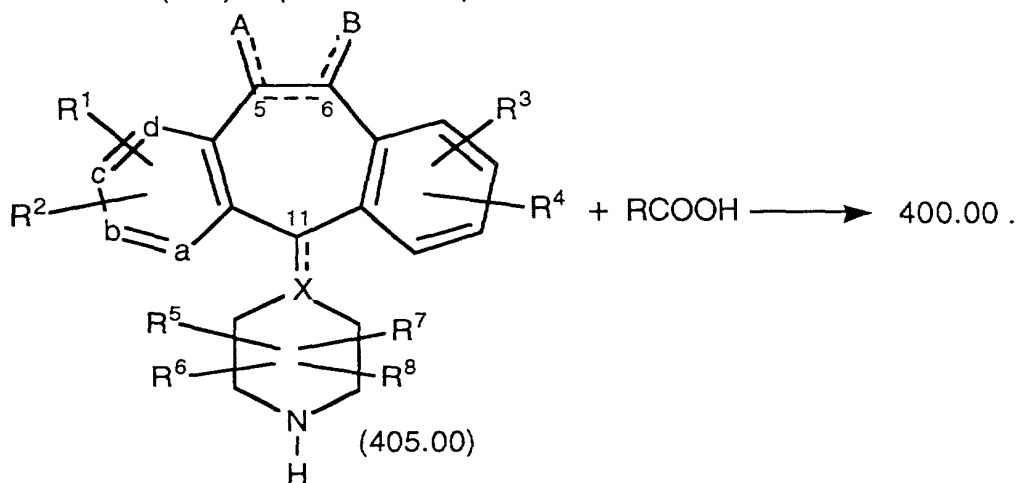


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wherein R represents R<sup>42</sup> or R<sup>44</sup>, and all other substituents are as described herein.

A. A compound of Formula 405.00 may be coupled with a compound of the formula RCOOH in the presence of coupling agent such as DEC, N,N'-dicyclohexylcarbodiimide (DCC) or N,N'-carbonyl-diimidazole (CDI) to produce compounds of Formula 400.00:

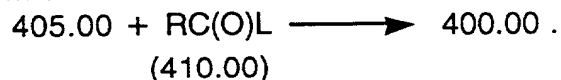
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The reaction is usually conducted in an inert solvent such as THF, DMF or CH<sub>2</sub>Cl<sub>2</sub> at a temperature between about 0°C and reflux, preferably at about room temperature. When the coupling agent is DCC or DEC, the reaction is preferably run in the presence of HOBT. Method A is the method of choice for preparing compounds of this invention.

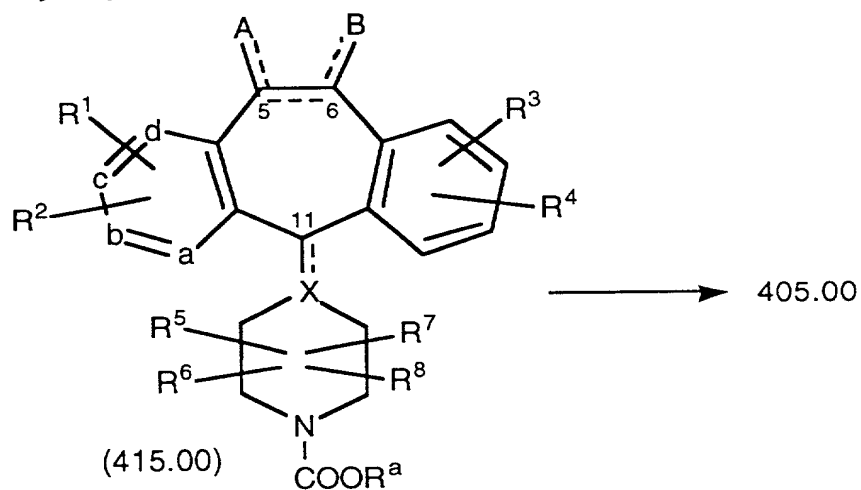
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B. A compound of Formula 405.00 may also be reacted with a compound of Formula 410.00 in the presence of base to produce compounds of Formula 400.00:



5 Representative examples of appropriate bases are pyridine and Et<sub>3</sub>N. L designates a suitable leaving group. For example, a compound of compound 410.00 may be an acyl halide (e.g., L represents halo) or an acyl anhydride, (e.g., L is -O-C(O)-R). The leaving group may also be alkoxy, in which case the compounds of Formula 400.00 may be produced  
10 by refluxing a compound of Formula 405.00 with an excess of a compound of Formula 410.00.

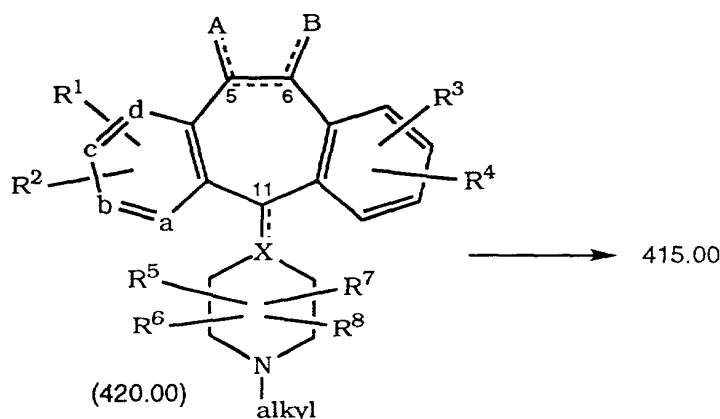
Compounds of Formula 405.00 may be prepared by cleaving the group COOR<sup>a</sup> from the corresponding carbamates 415.00, for example, via acid hydrolysis (e.g., HCl) or base hydrolysis (e.g., KOH):



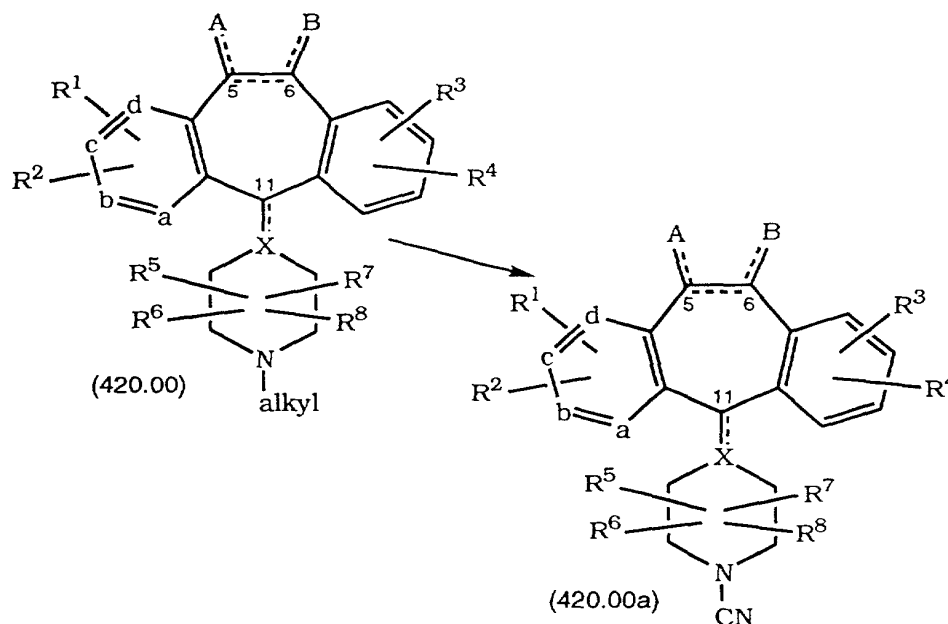
15 wherein R<sup>a</sup> is a group which does not prevent the cleavage reaction, e.g., R<sup>a</sup> is an optionally substituted alkyl such as ethyl.

Alternatively, depending upon the nature of R<sup>a</sup>, as determined by one skilled in the art, Compound 415.00 may be treated with an  
20 organometallic reagent (e.g., CH<sub>3</sub>Li), a reductive reagent (e.g., Zn in acid), etc., to form compounds of Formula 405.00.

Compound 415.00 may be prepared from the N-alkyl compound shown as Formula 420.00 below, in the manner disclosed in U.S. Patents 4,282,233 and 4,335,036.



It also will be apparent to one skilled in the art that there are other methods for converting Compound 420.00 to Compound 405.00. For example, treatment of Compound 420.00 with BrCN via von Braun reaction conditions would provide nitrile 420.00a. Subsequent hydrolysis of the nitrile under either aqueous basic or acidic conditions would produce Compound 405.00. This method is preferable when there is substitution on the piperidine or piperazine ring.



- 10 C. The compounds of Formula 400.00 wherein Z is O or S may be made by an alternative process using direct conversion of the N-alkyl compound 420.00 with an appropriate compound of Formula 410.00 such as an acyl halide or acyl anhydride. Preferably the reaction is run in the presence of an appropriate nucleophile (e.g. LiI, etc.) and solvent (e.g.,
- 15 toluene, dioxane or xylenes). An appropriate base, may be added, and

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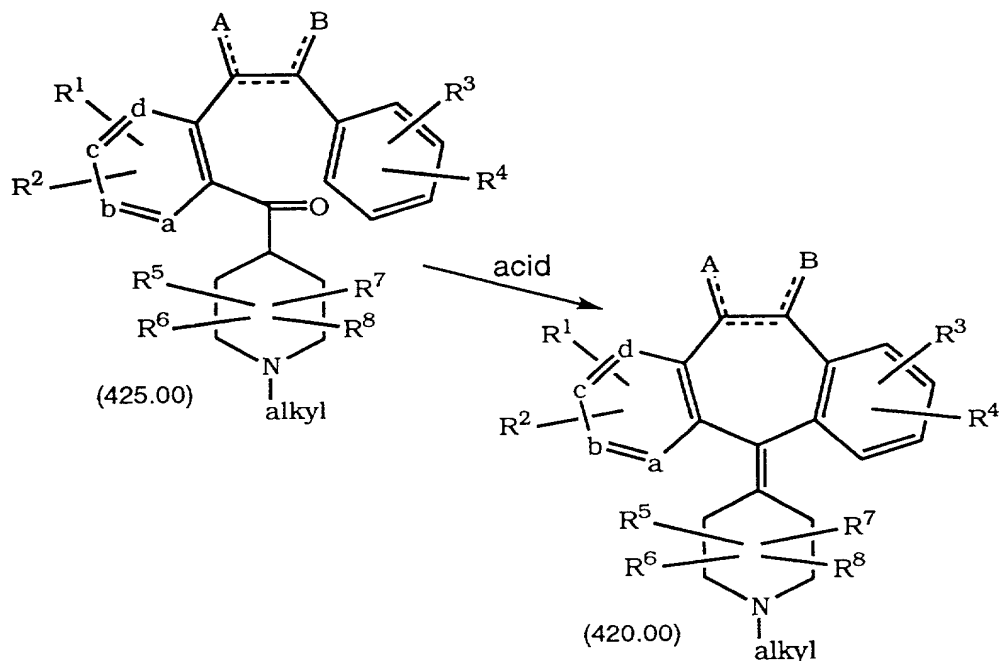
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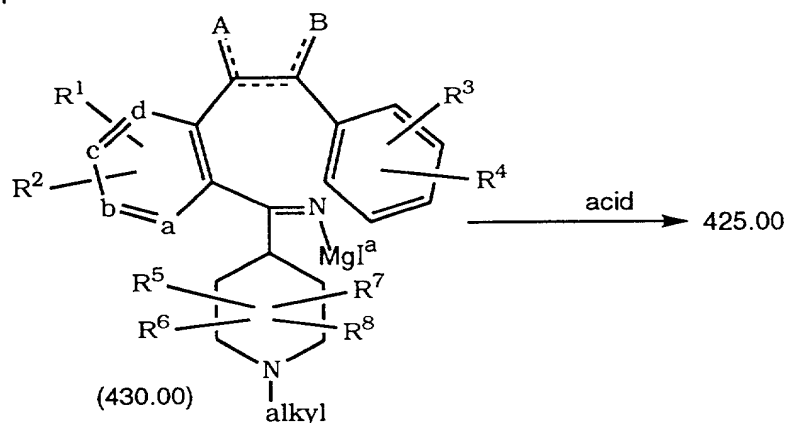
25°C to about 150°C and at lower temperatures but the reaction then takes longer to complete.

Generally the super acid is employed in excess, preferably in amounts of from about 1.5 to about 30 equivalents.



5

A ketone compound of Formula 425.00 may be formed by hydrolysis of 430.00, e.g., such as by reacting a Grignard intermediate of Formula 430.00 with an aqueous acid (e.g., aqueous HCl). I<sup>a</sup> in Formula 430.00 represents chloro, bromo or iodo.



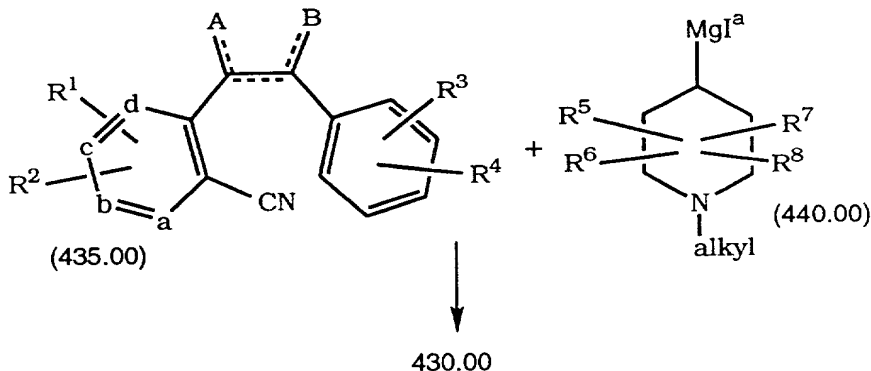
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The Grignard intermediate 430.00 is formed by the reaction of the cyano compound 435.00 with an appropriate Grignard reagent 440.00 prepared from 1-alkyl-4-halopiperidine. The reaction is generally performed in an inert solvent, such as ether, toluene, or THF, under

15 general Grignard conditions e.g., temperature of from about 0°C to about

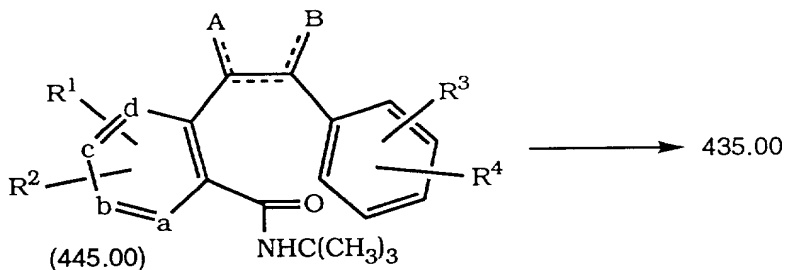


75°C. Alternatively, other organometallic derivatives of the 1alkyl-4-halo piperidine can be employed.

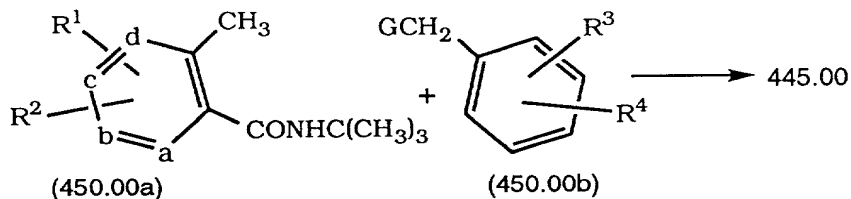


The cyano compound of Formula 435.00 is produced by converting the tertiary butyl amide of Formula 445.00 with a suitable dehydrating agent, such as  $\text{POCl}_3$ ,  $\text{SOCl}_2$ ,  $\text{P}_2\text{O}_5$ , toluene sulfonyl chloride in pyridine, oxalyl chloride in pyridine, etc. This reaction can be performed in the absence of or with a co-solvent, such as xylene.

The dehydrating agent such as  $\text{POCl}_3$  is employed in equivalent amounts or greater and preferably in amounts of from about 2 to about 15 equivalents. Any suitable temperature and time can be employed for performing the reaction, but generally heat is added to accelerate the reaction. Preferably the reaction is performed at or near reflux.



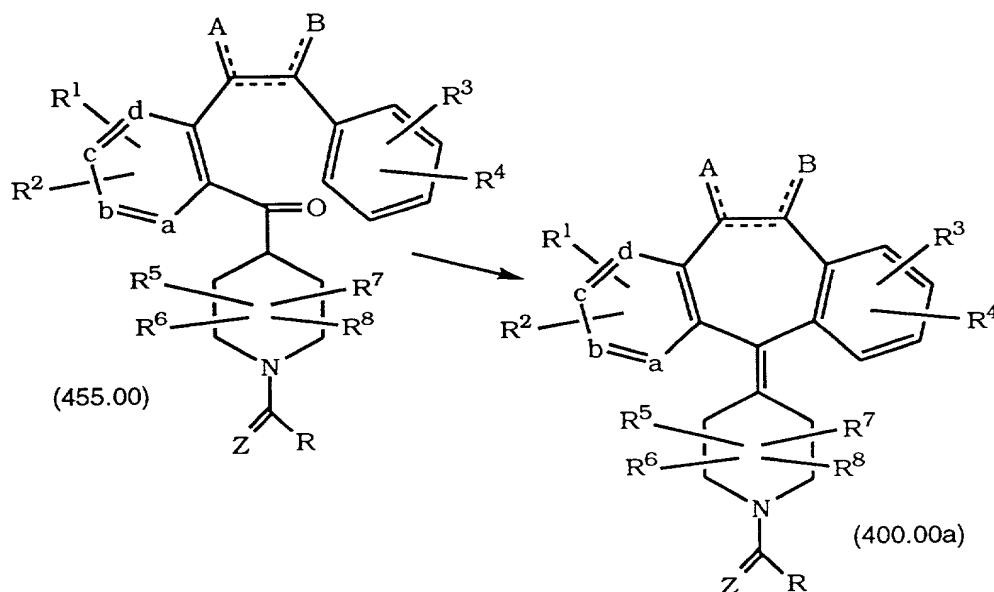
The tert-butylamide of Formula 445.00 may be produced by reaction of a compound of Formula 450.00a and 450.00b, in the presence of base, wherein G is chloro, bromo or iodo.



The compound of Formula 450.00a may be formed by hydrolysis of the corresponding nitrile wherein the appropriate cyanomethyl pyridine, such as 2-cyano-3-methylpyridine, is reacted with a tertiary butyl

compound in acid, such as concentrated sulfuric acid or concentrated sulfuric acid in glacial acetic acid. Suitable tertiary butyl compounds include, but are not limited to, t-butyl alcohol, t-butyl chloride, t-butyl bromide, t-butyl iodide, isobutylene or any other compound which under hydrolytic conditions forms t-butyl carboxamides with cyano compounds. The temperature of the reaction will vary depending upon the reactants, but generally the reaction is conducted in the range of from about 50°C to about 100°C with t-butyl alcohol. The reaction may be performed with inert solvents, but is usually run neat.

10 An alternative process for the formation of compounds of Formula 400.00a may involve direct cyclization of Compound 455.00 as shown below.

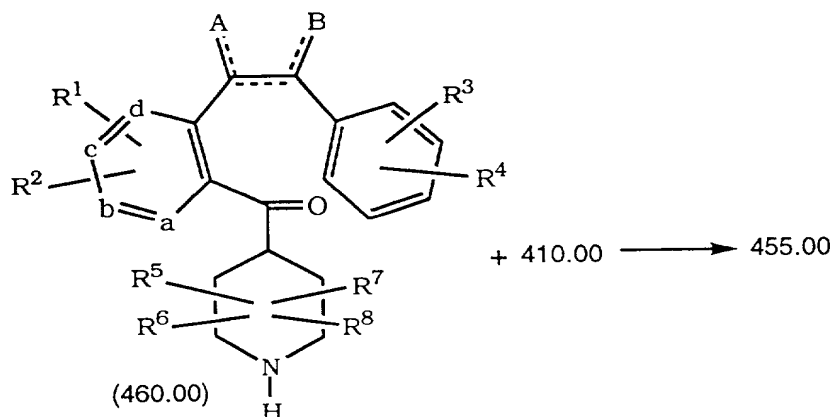


15 Cyclization to form the cycloheptene ring may be accomplished with a strong acid (e.g., triflic, polyphosphoric, HF/BF<sub>3</sub>), and may be performed in an inert solvent, such as ether, toluene or THF. The temperature and time may vary with the acid employed, as described in process A above.

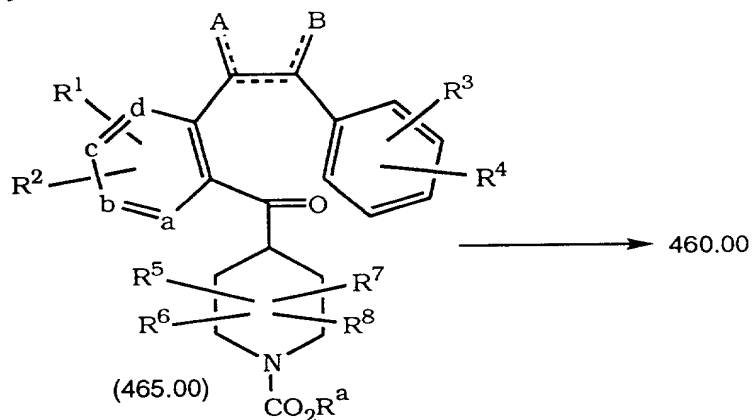
20 Compounds of Formula 455.00 wherein Z = O or S may be prepared by treating a compound of Formula 425.00 with an appropriate acyl halide or acyl anhydride of formula 410.00. Most preferably this reaction is run in the presence of a good nucleophile, such as LiI, in the appropriate solvent, such as toluene, dioxane or xylene, and at a temperature ranging from 50-150°C, preferably 100-120°C.



- A second method of preparing compounds of Formula 455.00 involves reacting an unsubstituted piperidylidene compound of Formula 460.00 with the appropriate acyl halide or acyl anhydride of Formula 410.00 in the presence of base, such as pyridine or Et<sub>3</sub>N. Alternatively, if
- 5 L = OH in compound 410.00, then coupling of compound 460.00 with compound 410.00 may require use of a conventional coupling reagent, such as DCC or CDI.



- Compounds of Formula 460.00 may be produced from the
- 10 corresponding carbamates of Formula 465.00, via acid hydrolysis, using for example, aqueous HCl, or base hydrolysis using for example, KOH. Alternatively, some compounds can be prepared by treating the carbamate, Formula 465.00, with an organometallic reagent, such as
- 15 methyl lithium or a reductive reagent, such as zinc in acid, etc., depending upon the nature of the R<sup>a</sup> group. For example, if R<sup>a</sup> is a simple alkyl group, CO<sub>2</sub>R<sup>a</sup> may be cleaved by alkaline hydrolysis at 100°C.



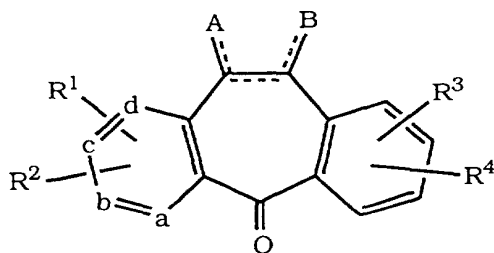
- The carbamate compounds of Formula 465.00 may be prepared from the appropriate alkyl compound of Formula 425.00 by treatment with
- 20 a chloroformate, preferably in an inert solvent, such as toluene, with

warming to approximately 80°C. Other alternative methods are available for the conversion of 425.00 to 455.00 as previously described (e.g. Von Braun reaction conditions). Compounds of Formula 425.00 may be prepared as described above.

5

### SUBSTITUTION ON THE PYRIDINE RING

Various methods can be used as described in WO 88/03138 to provide compounds which are substituted on the pyridine ring, i.e., in positions 2-, 3- and or 4- positions of the tricyclic ring system. For example, the cyclization methods described on pages 20-30 of WO 88/03138 can already have the appropriate substituents on the pyridine ring in place. A variety of substituted pyridines are known in the literature and can be employed in these syntheses. Alternatively, the azaketone of Formula XIX (from page 27 of WO 88/03138)



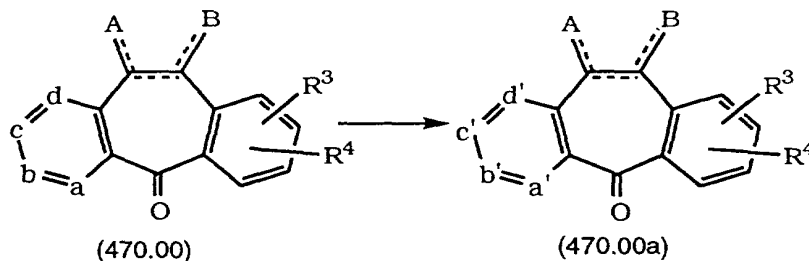
(XIX) p.27 WO88/03138

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wherein R<sup>1</sup> and R<sup>2</sup> are both H can be converted to the appropriately substituted azaketone wherein R<sup>1</sup> and R<sup>2</sup> are non-H substituents. If both R<sup>1</sup> and R<sup>2</sup> are desired to be non-H substituents the procedure would be repeated.

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The azaketone is thus reacted with an oxidizing agent such as meta-chloroperoxybenzoic acid (MCPBA) or hydrogen peroxide to produce the corresponding compound in which the nitrogen of the pyridine ring is as an N-oxide:

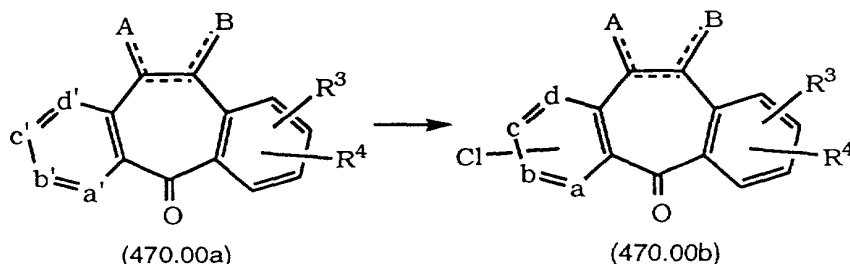


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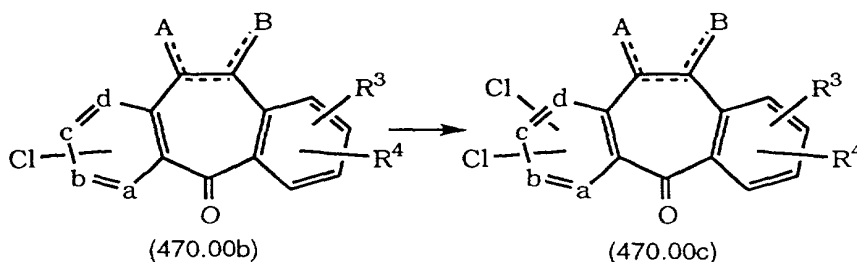
wherein one of a', b', c' or d' is N→O and the others are CH or CR<sup>1</sup> or CR<sup>2</sup>. This reaction is normally run at temperatures from -15°C to reflux, more typically at about 0°C. The reaction is preferably conducted in an

inert solvent such as  $\text{CH}_2\text{Cl}_2$  for MCPBA or acetic acid for hydrogen peroxide.

- 5 The azaketone N-oxide of Formula 470.00a can then be reacted with a chlorinating agent such as  $\text{SO}_2\text{Cl}_2$  or  $\text{SOCl}_2$  to form a compound of Formula 470.00b. Typically, this reaction results in monosubstitution of Cl in the ortho or para-position relative to the N atom of the ring.



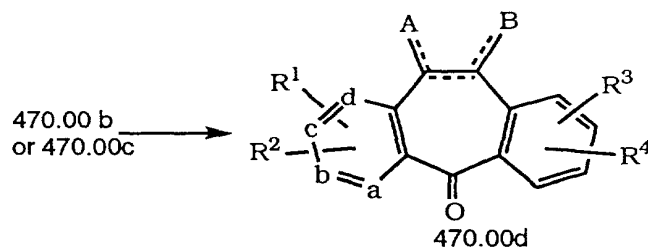
To provide the disubstituted products, steps 1 and 2 above are repeated.



10

Typically, the resulting disubstituted compounds have Cl ortho and para relative to the N atom of the pyridine ring.

- 15 The mono or disubstituted compounds of Formulas 470.00b and 470.00c above can be reacted with various nucleophiles such as alkoxides, amines, thiols, etc. This will result in compounds where one or both of the Cl substituents are replaced by the nucleophile to provide a compound of Formula 470.00d or a compound easily converted to Formula 470.00d.



20

The substituted ketone of Formula 470.00 can then be converted to the desired compound by the methods described above and in WO 88/03138 and in U.S. Patent No. 3,326,924.

(415.00)  $\xrightarrow{\hspace{1cm}}$  (415.01)

Alternatively, the Cl substituted azaketones of Formula 470.00b or 470.00c above can be converted to the corresponding derivatives of Formula 405.00 above wherein R<sup>1</sup> and/or R<sup>2</sup> is Cl by methods analogous to those described above. At this point the Cl substituent(s) can be displaced by an appropriate nucleophile to provide the desired substituent. Suitable nucleophiles include alkoxide, amines, thiols, etc. This reaction usually requires higher temperatures (e.g., from about 100° to about 200°C) than the displacement reaction to produce ketone 470.00d above. It is also usually conducted in a sealed vessel in an inert solvent. The compound of Formula 405.00 is then converted to a compound of Formula 400.00 as described above.

25 An alternative process for introducing substituents at the C-3  
position of pyridine Ring I of Formula 1.0, involves nitrating a compound  
of Formula 415.00 (except wherein X is nitrogen) or a compound of  
Formula 470.00d with tetrabutylammonium nitrate - TFAA in CH<sub>2</sub>Cl<sub>2</sub> at a  
temperature of 0°C to room temperature (about 25°C). The nitro group  
30 may then be reduced to the corresponding amine using iron filings in

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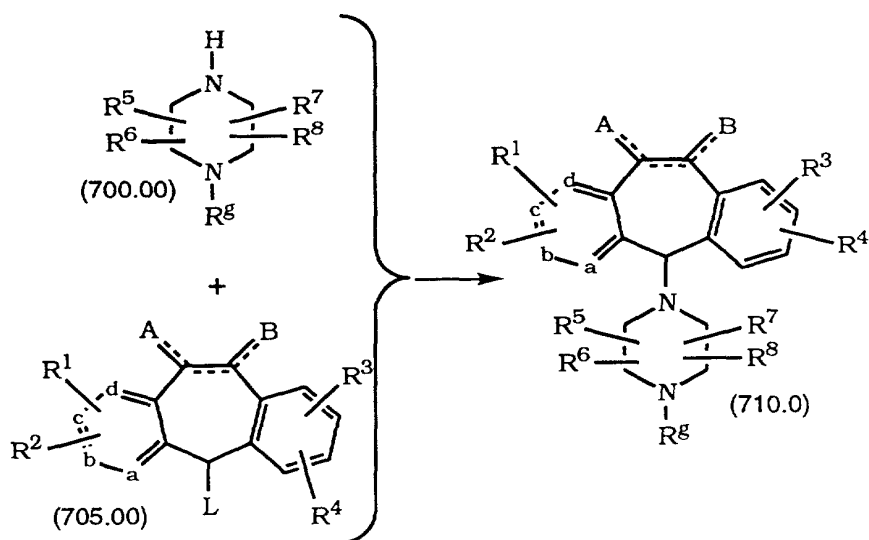
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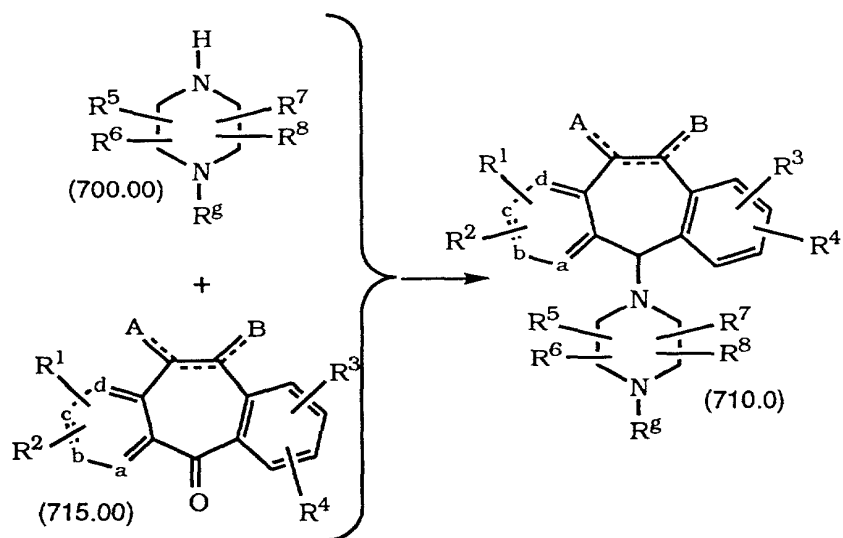
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In this reaction R<sup>g</sup> is H, CO<sub>2</sub>R<sup>a</sup> (wherein R<sup>a</sup> is a C<sub>1</sub> to C<sub>4</sub> alkyl group) or C(Z)R. The preparation of compound 705.00 wherein L is Cl is analogous to the procedure described in U.S. 3, 409,621. One skilled in the art can prepare other derivatives of 705.00 (e.g., L is Br, I, mesyloxy, or tosyloxy). When R<sup>g</sup> is H, C(Z)R or CO<sub>2</sub>R<sup>a</sup>, these are converted to compounds of the invention by processes known in the art.

An alternate route for generating the compound of Formula 710.00 is by reductive amination of the aza ketone 715.00 with the piperazine





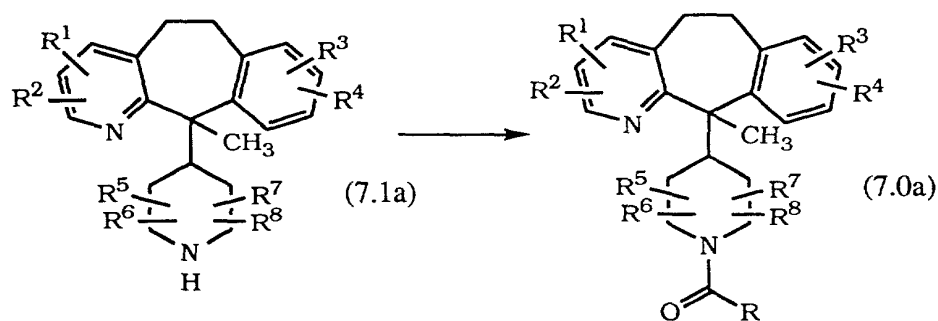
The reaction is typically carried out in a polar solvent, such as MeOH or EtOH, optionally in the presence of a dehydrating agent, such as 3Å molecular sieves. The intermediate Schiff base can be reduced to the compound of Formula 710.00 by employing a variety of reducing agents, such as NaCNBH<sub>3</sub>, or catalytic hydrogenation, for example, hydrogen over Pd/C.

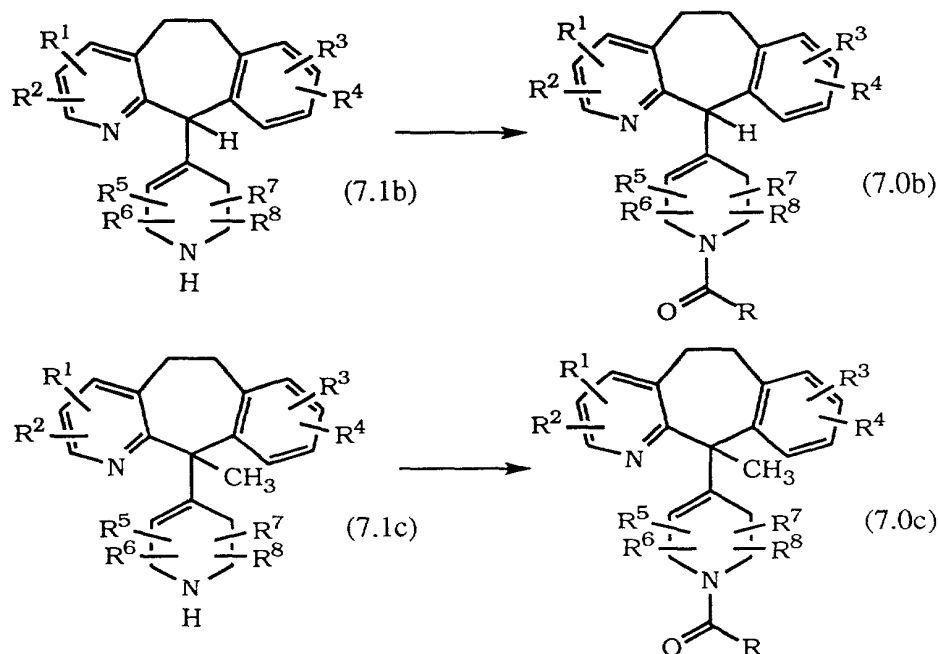
When R<sub>9</sub> is C(Z)R, these are the compounds of the invention. When R<sub>9</sub> is H or CO<sub>2</sub>R<sup>a</sup>, these are converted to compounds of the invention as described herein.

Compounds of Formulas 5.3A and 5.3B, wherein R<sup>25</sup> represents a pyridyl N-oxide, can be produced by reacting compounds of Formulas 5.3A and 5.3B, wherein R<sup>25</sup> is pyridyl, with a one molar equivalent of an oxidizing agent (such as oxone).

Compounds of Formulas 5.3, 5.3A and 5.3B, wherein R<sup>25</sup> represents a pyridyl N-oxide, can be produced by reacting the product of Preparative Example 12 with a peroxyacid (such as MCPBA) to give the corresponding N-oxide intermediate. The desired N-oxide product may be obtained from the N-oxide intermediate by following the procedure of Example 183.

Compounds of the formula 7.0a, 7.0b and 7.0c can be prepared from amines of the formula 7.1a, 7.1b and 7.1c, respectively, by coupling a compound of the formula 7.0a, 7.0b or 7.0c with a carboxylic acid of the formula RCOOH via the method described above for reacting compounds of the formula 405.00.



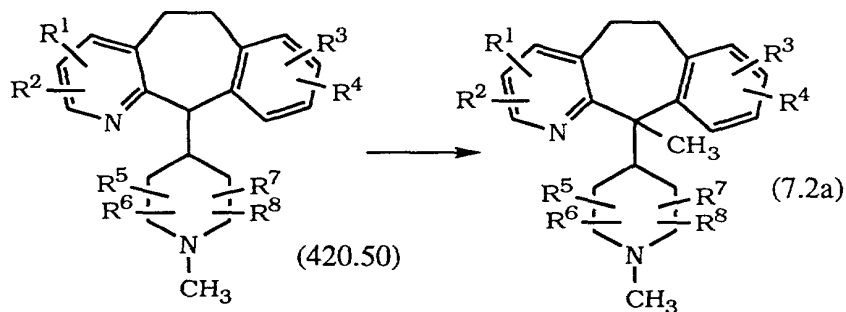


Alternatively, a compound of the formula 7.0a, 7.0b or 7.0c is  
 5 treated with a compound of the formula  $RC(O)L$ , where L is a suitable  
 leaving group, via the procedure described above for compounds of the  
 formula 405.00.

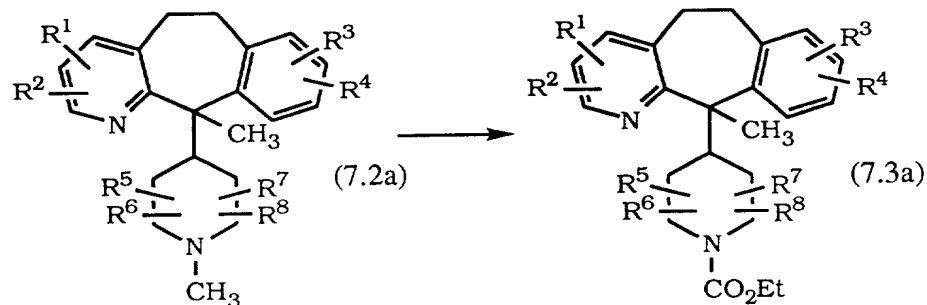
Compounds of the formula 7.1a can be prepared from a compound  
 of the formula 420.50, (i.e., a compound of the formula 420.00 wherein A  
 and B are both H, no double bond is present between carbons 5 and 6, or  
 10 between carbon 11 and X, X is CH, and the N-alkyl group is a methyl  
 group) as shown in Reaction Scheme 1.

#### Reaction Scheme 1

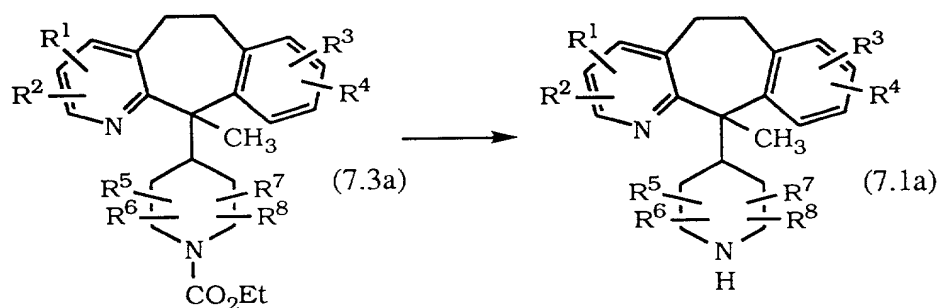
Step A:



Step B:



Step C:



5

In Step A of Reaction Scheme 1, a compound of the formula 420.50 is reacted with a strong base, such as an lithium diisopropylamide or an alkyllithium reagent (e.g., n-butyllithium), at -100° to -10°C, preferably at -80° to -20°C, then treated with methyl iodide to form a compound of formula 7.2a.

In Step B of Reaction Scheme 1, a compound of the formula 7.2a is converted to a compound of the formula 7.3a via substantially the same procedure as described above for formation of compounds of the formula 415.00.

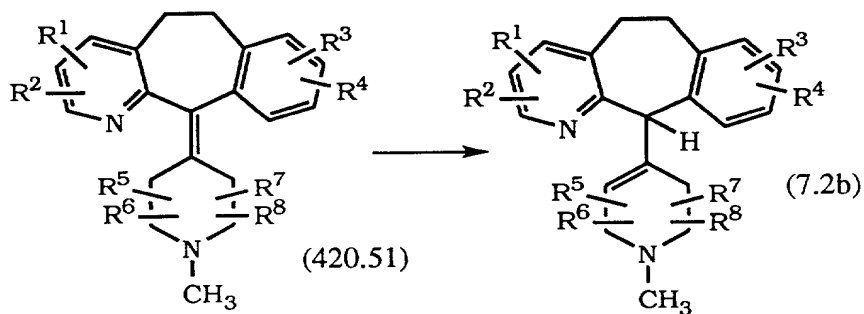
In Step C of Reaction Scheme 1, a compound of the formula 7.3a is hydrolyzed via essentially the same procedure as described above for formation of compounds of formula 405.00, to form a compound of the formula 7.1a.

Compounds of the formula 7.1b can be prepared from a compound of the 420.51 (i.e., a compound of the formula 420.00 wherein A and B are both H, no double bond is present between carbons 5 and 6, a double bond is present between carbon 11 and X, X is C, and the N-alkyl group is a methyl group) via the process shown in Reaction Scheme 2.

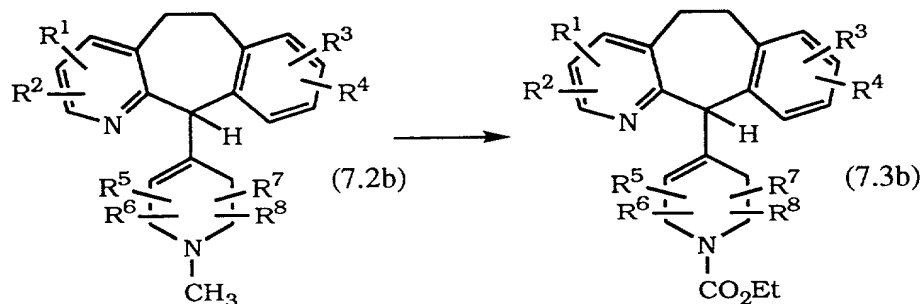
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Reaction Scheme 2

Step A:

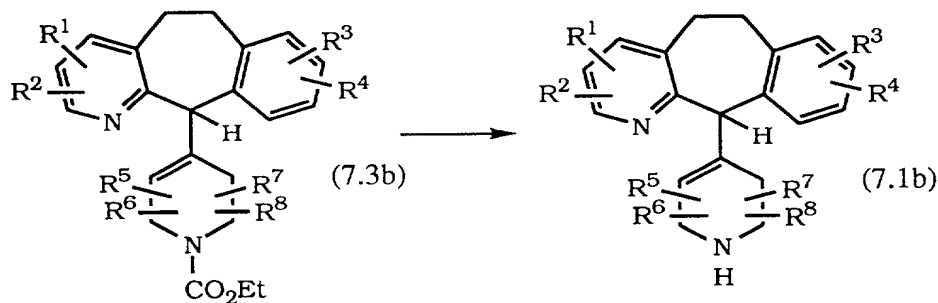


Step B:



5

Step C:



10 In Step A of Reaction Scheme 2, a compound of the formula 420.51 is reacted with a strong base, such as an lithium diisopropylamide or an alkyllithium reagent (e.g., n-butyllithium), at -100° to -10°C, preferably at -80° to -20°C, then treated with a protic solvent, such as an alcohol, preferably MeOH, to form a compound of formula 7.2b.

15 In Step B of Reaction Scheme 2, a compound of the formula 7.2b is converted to a compound of the formula 7.3b via substantially the same procedure as described above for formation of compounds of the formula 415.00.

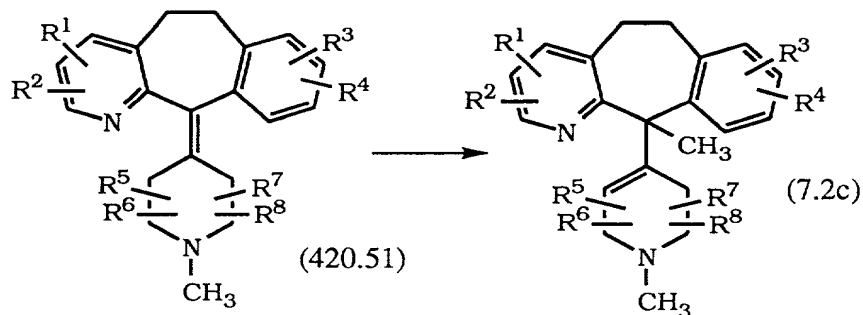
In Step C of Reaction Scheme 2, a compound of the formula 7.3b is hydrolyzed via essentially the same procedure as described above for

formation of compounds of formula 405.00, to form a compound of the formula 7.1b.

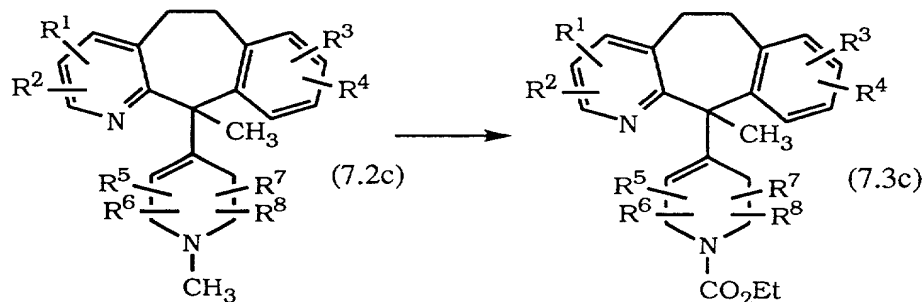
Compounds of the formula 7.1c can be prepared from a compound of the 420.51 via the process shown in Reaction Scheme 3.

### Reaction Scheme 3

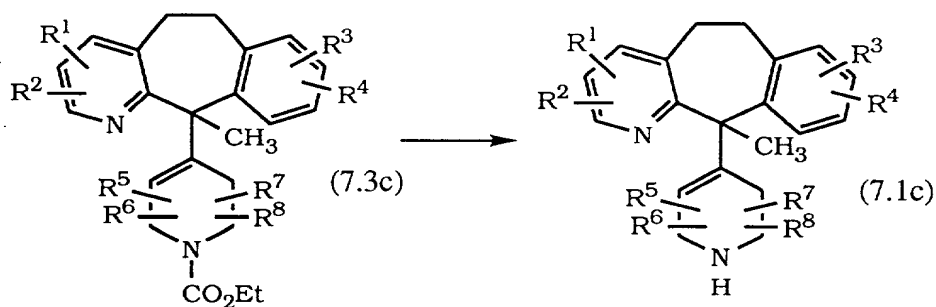
Step A:



Step B:



Step C:



In Step A of Reaction Scheme 3, a compound of the formula 420.51 is reacted with a strong base, such as an lithium diisopropylamide or an alkyllithium reagent (e.g., n-butyllithium), at  $-100^{\circ}$  to  $-10^{\circ}\text{C}$ , preferably at  $-80^{\circ}$  to  $-20^{\circ}\text{C}$ , then treated with methyl iodide to form a compound of formula 7.2c.

In Step B of Reaction Scheme 3, a compound of the formula 7.2c is converted to a compound of the formula 7.3c via substantially the same

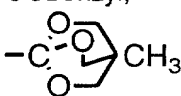





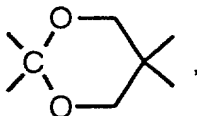
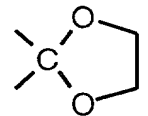
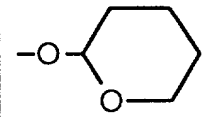
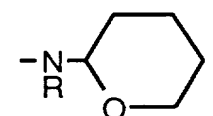

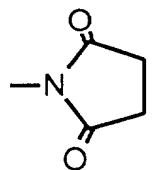
procedure as described above for formation of compounds of the formula 415.00.

- 5 In Step C of Reaction Scheme 1, a compound of the formula 7.3c is hydrolyzed via essentially the same procedure as described above for formation of compounds of formula 405.00, to form a compound of the formula 7.1c.

- 10 In the above processes, it is sometimes desirable and/or necessary to protect certain  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^4$  etc., groups during the reactions. Conventional protecting groups are operable as described in Greene, T.W., "Protective Groups In Organic Synthesis," John Wiley & Sons, New York, 1981. For example, the groups listed in column 1 of Table 1 may be protected as indicated in column 2 of the table:

Table 1

**TABLE 1**  
**PROTECTED GROUPS**

| 1. GROUP TO BE PROTECTED  | 2. PROTECTED GROUP   |
|---|--|
| -COOH   | -COOalkyl, -COObenzyl,<br>-COOphenyl,   |
|    |  ,  ,<br> |
|    |  ,   |
| -OH   |  , -OCH <sub>2</sub> phenyl,<br>-OCH <sub>3</sub> , OSi(CH <sub>3</sub> ) <sub>2</sub> (t-Bu),   |
| -NHR, wherein R is any substituent on an amino group within the scope of the claims |  ,<br>-NR-CO-CF <sub>3</sub> , -NRCOCH <sub>3</sub> ,<br>-NRCH <sub>2</sub>            |
| -NH <sub>2</sub>  |  ,<br>-NH-C(O)-O(t-Bu)  |

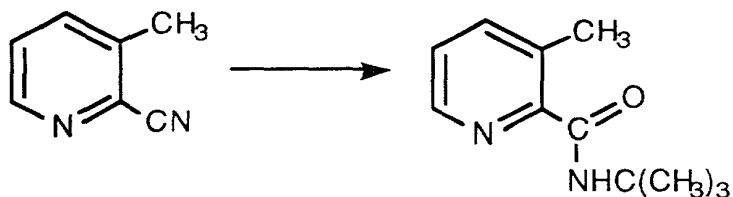
Other protecting groups well known in the art also may be used. After the reaction or reactions, the protecting groups may be removed by standard procedures.

Compounds useful in this invention are exemplified by the following preparative examples, which should not be construed to limit the scope of the disclosure. Alternative mechanistic pathways and analogous

structures within the scope of the invention may be apparent to those skilled in the art.

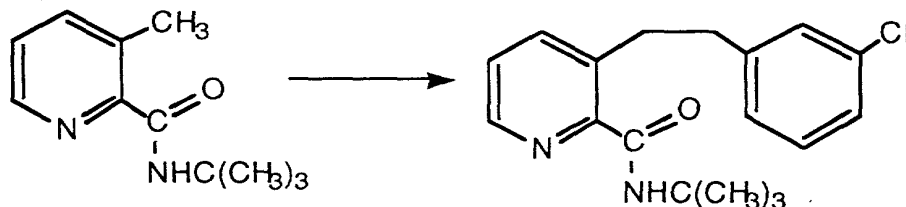
PREPARATIVE EXAMPLE 1

5           A.    N-(1,1-DIMETHYLETHYL)-3-METHYL-2-PYRIDINE  
CARBOXAMIDE



Suspend 2-cyano-3-methyl pyridine (400 g) in t-butanol (800 mL) and heat to 70°C. Add concentrated sulphuric acid (400 mL) dropwise over 45 minutes. Maintain the temperature at 75°C, until the reaction is complete, and for an additional 30 minutes. Dilute the mixture with water (400 mL), charge with toluene (600 mL) and bring to pH 10 with concentrated aqueous ammonia. Maintain the temperature at 50-55°C during the work up. Separate the toluene phase, and reextract the aqueous layer. Combine toluene phases and wash with water. Remove the toluene to yield the title compound N-(1,1-dimethylethyl)-3-methyl-2-pyridine carboxamide, as an oil, from which solid product is crystallized. (Yield 97%, as determined by an internal standard assay with gas chromatography).

20           B.    3-[2-(3-CHLOROPHENYL)ETHYL]-N-(1,1-DIMETHYL-  
ETHYL)-2-PYRIDINE CARBOXAMIDE

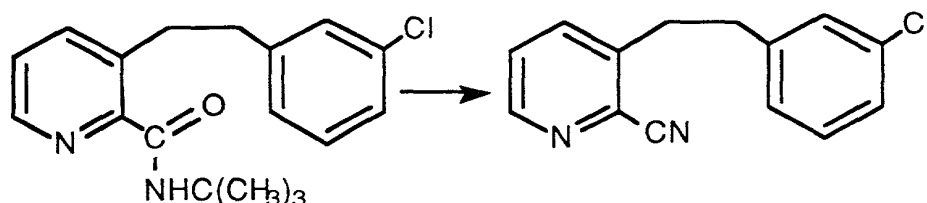


Dissolve the title compound of Preparative Example 1A, N-(1,1-dimethylethyl)-3-methyl-2-pyridine carboxamide (31.5 g.) in THF (600 mL) and cool the resulting solution to -40°C. Add n-butyllithium (2 eq.) in hexane while maintaining the temperature at -40°C. The solution turns deep purple-red. Add sodium bromide (1.6 g) and stir the mixture. Add solution of m-chlorobenzylchloride (26.5 g., 0.174 mole) in THF (125 mL) while maintaining the temperature at -40°C. Stir the reaction mixture until the reaction is complete as determined by thin layer chromatography. Add



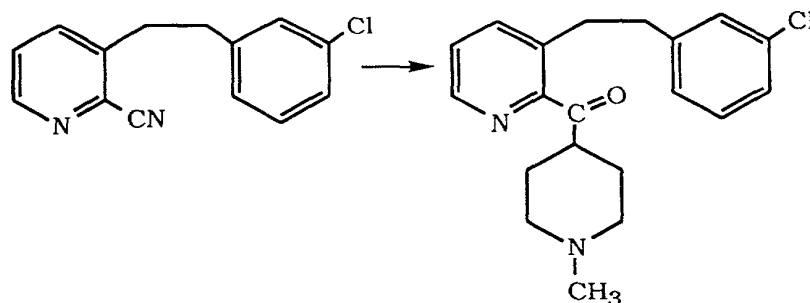
water to the reaction until the color is dissipated. Extract the reaction mixture with EtOAc, wash with water, and concentrate to a residue which is the title compound. (Yield 92% as shown by chromatography).

5 C. 3-[2-(3-CHLOROPHENYL)ETHYL]-2-PYRIDINE-CARBO-  
NITRILE



Heat a solution of the title compound of Preparative Example 1B, 3-[2-(3-chlorophenyl)ethyl]-N-(1,1-dimethylethyl)-2-pyridine carboxamide (175 g, 0.554 mole) in phosphorous oxychloride (525 mL, 863 g, 5.63 mole) and reflux for 3 hours. Determine completion of the reaction by thin layer chromatography. Remove any excess phosphorous oxychloride by distillation at reduced pressure and quench the reaction in a mixture of water and isopropanol. Bring to pH 5-7 by adding 50% aqueous NaOH solution while maintaining the temperature below 30°C. Filter the crystalline slurry of crude product and wash with water. Purify the crude product by slurrying the wet cake in hot isopropanol, and cool to 0-5°C. Filter the product, wash with hexane and dry at a temperature below 50°C to yield the title compound. (Yield: 118g (HPLC purity 95.7%), m.p. 72°C-73°C, 89.4% of theory).

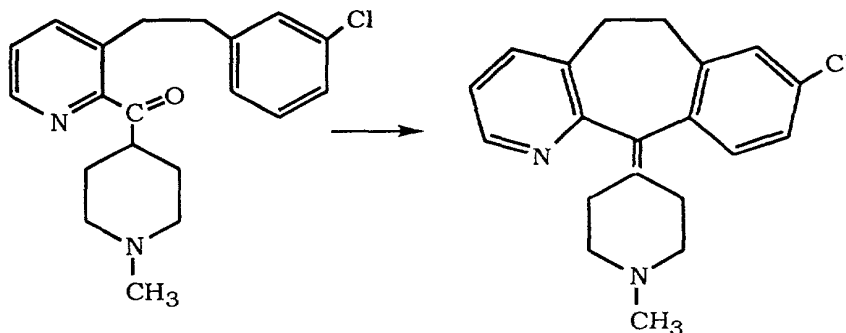
20 D. 1-(METHYL-4-PIPERIDINYL)[3-(2-(3-CHLORO-  
PHENYL)ETHYL)-2-PYRIDINYL]METHANONE HYDROCHLORIDE



Dissolve the title compound of Preparative Example 1C, (118 g, 0.487 mole) in dry THF (1.2L) and add N-methyl-piperidyl magnesium chloride (395 mL, 2.48 mole/liter, 0.585 mole, 1.2 eq.) over 15 minutes. Maintain the temperature at 40°C-50°C by cooling with water as necessary, for 30 minutes. Determine completion of the reaction by thin layer chromatography. Quench the reaction by reducing the pH to below

- 2 with 2N HCl and stir the resulting solution at 25°C for 1 hour. Remove the bulk of the THF by distillation and adjust the resulting solution to pH 3.5 by addition of aqueous NaOH. Cool to 0 to 5°C and filter off the crystalline hydrochloride salt product. Wash with ice cold water and dry to constant weight at 60°C to yield the title compound. (Yield: 168.2 g (HPLC purity 94%), m.p. 183°-185°C, 89% of theory).

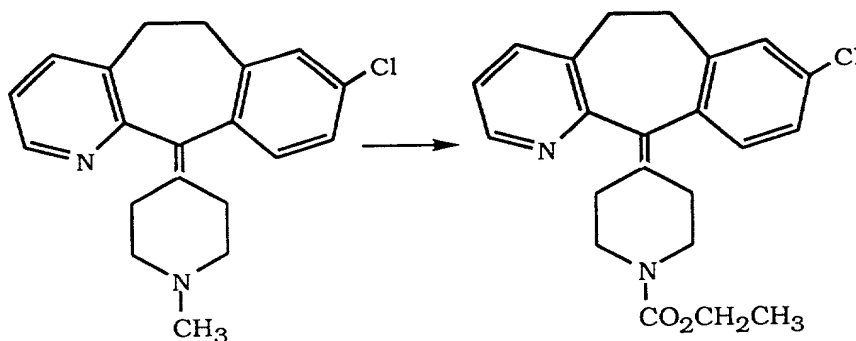
E. 8-CHLORO-11-(1-METHYL-4-PIPERIDYLIDENE)-6,11-DIHYDRO-5H-BENZO[5.6]CYCLOHEPTA[1.2-b]PYRIDINE



- 10 Dissolve the title compound of Preparative Example 1D above (59 g, 0.15 mole) in hydrofluoric acid (120 mL, 120 g, 6.0 mole) at -35°C and add boron trifluoride (44.3 g, 0.66 mole) over 1 hour. Determine completeness of the reaction by thin layer chromatography. Quench the reaction using ice, water and KOH bringing the solution to a final pH of 10.
- 15 Extract the product with toluene and wash with water and brine. Concentrate the toluene solution to a residue, and dissolve in hot hexane. Remove the insolubles by filtration and concentrate the filtrate to yield the title compound as an off-white powder. (Yield: 45.7 g (HPLC purity: 95%), 92% of theory).
- 20 Alternative Step E: 8-CHLORO-11-(1-METHYL-4-PIPERIDYLIDENE)-6,11-DIHYDRO-5H-BENZO[5.6]CYCLOHEPTA[1.2-b]PYRIDINE
- 25 React the title compound of Preparative Example 1D above (177 g, 0.49 mole) in trifluoromethanesulfonic acid (480 ml, 814.1 g, 5.31 mole) at 90-95°C for 18 hours under nitrogen. Determine the completeness of the reaction by thin layer chromatography. Cool the reaction and quench the reaction with ice-water and adjust the pH to 6 with barium carbonate. Extract the product with CH<sub>2</sub>Cl<sub>2</sub>, and concentrate under reduced pressure to about 1 liter. Wash with water, and extract the product into 1 N HCl
- 30 which is treated with 30 g of activated charcoal, and filter through celite. Adjust the pH of the filtrate to 10 with aqueous NaOH (50%), extract the

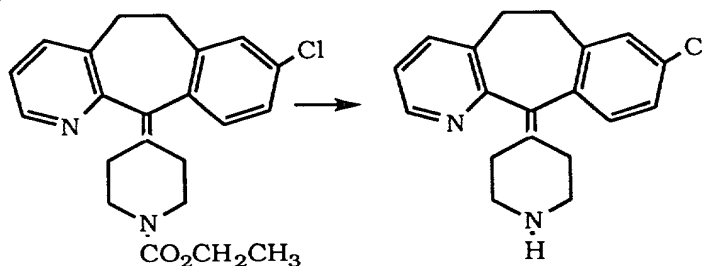
product into  $\text{CH}_2\text{Cl}_2$ , and remove under reduced pressure to form a residue. Dissolve the residue in hot hexane, and filter to remove insolubles. Concentrate the filtrate to yield the title compound as a beige powder. (Yield: 126 g (HPLC purity 80%), 65% of theory).

5 F. 8-CHLORO-11-(1-ETHOXYCARBONYL-4-PIPERIDYLIDENE)-6,11-DIHYDRO-5H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDINE

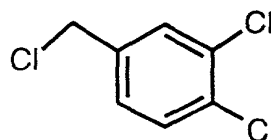


Dissolve the title compound of Preparative Example 1E above (45.6 g, 0.141 mole) in toluene (320 mL) at  $80^\circ\text{C}$  and to it gradually add ethyl chloroformate (40.4 mL, 45.9 g, 0.423 mole). Following complete addition, maintain the temperature at  $80^\circ\text{C}$  for 1 hour, then add diisopropylethylamine (2.7 mL, 2.00 g, 0.016 mole) and additional ethyl chloroformate (4.1 mL, 4.65 g, 0.0429 mole). Monitor completeness of the reaction by thin layer chromatography. Upon completion, cool the reaction mixture to ambient temperature, and wash the toluene solution with water. Concentrate the organic layer to a residue and dissolve in hot acetonitrile (320 mL). Decolorize the solution with 14 g of activated charcoal. Remove the activated charcoal by filtration and concentrate the filtrate to a crystalline slurry. Cool the mixture to  $0-5^\circ\text{C}$ , and isolate the product by filtration. Wash with cold acetonitrile and dry the product at below  $70^\circ\text{C}$  to yield the title compound. (Yield: 42.4 g (HPLC purity 97.4%), 80% of theory).

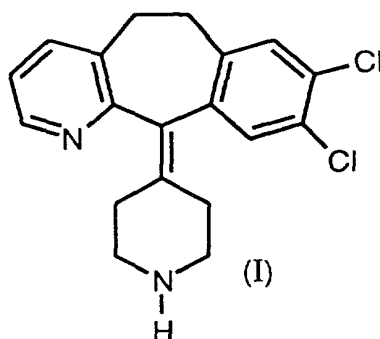
25 G. 8-CHLORO-11-(4-PIPERIDYLIDENE)-6,11-DIHYDRO-5H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDINE



- Hydrolize the title compound of Preparative Example 1F, 8-chloro-11-(1-ethoxycarbonyl-4-piperidylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine (39 g, 0.101 mole) with KOH (50 g) in EtOH (305 mL) and water (270 mL) at reflux under an argon atmosphere for 64 hours. Partially distill off the EtOH and dilute the residue with brine, and extract with EtOAc (3x). Wash the combined organic phases with water and dry with Na<sub>2</sub>SO<sub>4</sub>. Remove the solvent to give a solid which can be recrystallized from toluene to give the title compound as a white solid. (Yield: 24.5 g, 77%, melting point 154-155°C).
- 10 H. By substituting in step 1B above, the benzylic halide:



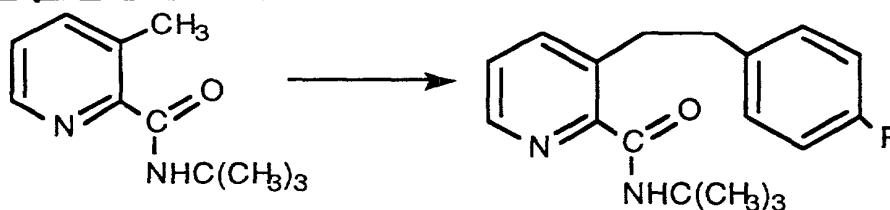
for meta-chlorobenzylchloride, and employing basically the same methods as steps C through G, the compound



- 15 is prepared. Dichloro compound (I) is recrystallized from toluene and has a melting point of 150-152°C. Reaction times are determined by TLC or HPLC. In some instances purification of the product by chromatography is necessary.

20 PREPARATIVE EXAMPLE 2

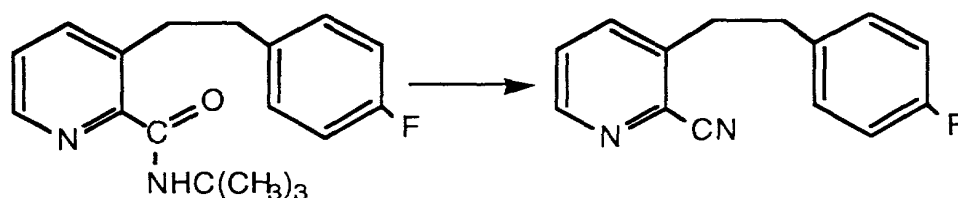
A. N-(1,1-DIMETHYLETHYL)-3-[2-(4-FLUOROPHENYL)-ETHYL]-2-PYRIDINE CARBOXAMIDE



Cool a solution of N-(1,1-dimethylethyl)-3-methyl-2-pyridine-carboxamide (38.4 g, 0.2 mole) in dry THF (250 mL) to -40°C and add n-butyl lithium (185 mL, 0.44 mole). Add sodium bromide (1.9 g, 18 mmol.) and stir for 15 minutes. Add 4-fluorobenzylchloride (31.8 g, 0.22 mole) and stir for 2.5 hours while warming to -5°C. Quench the reaction with water and extract the product twice with EtOAc, then wash with brine (2X). Dry the organic phase over Na<sub>2</sub>SO<sub>4</sub>, filter and remove the solvent to give the title compound. (60.0 g, Yield 99%, m.p. 59-61°C.)

B. 3-[2-(4-FLUOROPHENYL)ETHYL]-2-PYRIDINE

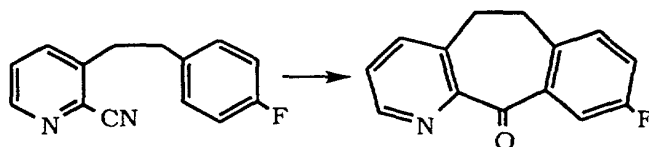
10 CARBONITRILE



Heat the title compound of Preparative Example 2A above (60.0 g, 0.2 mole) in POCl<sub>3</sub> (200 mL) to 110°C under an argon atmosphere for 3.5 hours. Pour the reaction mixture onto ice and basify with NaOH (50%) solution. Extract the mixture with EtOAc (3x) and wash with water. Wash with brine and dry over Na<sub>2</sub>SO<sub>4</sub>. Remove the solvent and pass the residue through a coarse SiO<sub>2</sub> (60-200 mesh) column to give the title compound as a white solid (40 g, Yield 88%, m.p. 48- 49°C.).

C. 9-FLUORO-5,6-DIHYDRO-11H-BENZO[5,6]CYCLOHEPTA-[1,2-b]PYRIDIN-11-ONE

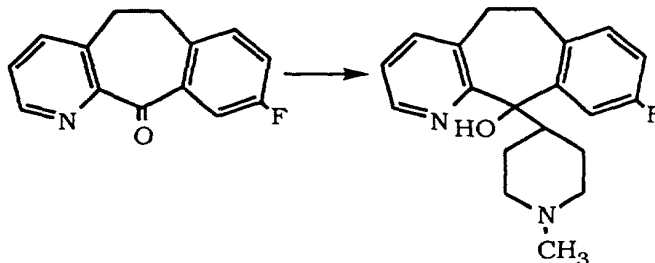
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Cyclize the title compound of Preparative Example 2B above (31.5 g, 139 mmol) in polyphosphoric acid (1.24 kg) at 200°C for 5.5 hours. Pour onto ice and basify with NaOH solution (50%). Extract the product with chloroform (3x) and wash with brine. Dry the organic phase with Na<sub>2</sub>SO<sub>4</sub>, filter and remove the solvent to give the title compound (20.4 g, yield 64%, m.p. 78-81°C after recrystallization from diisopropyl ether).

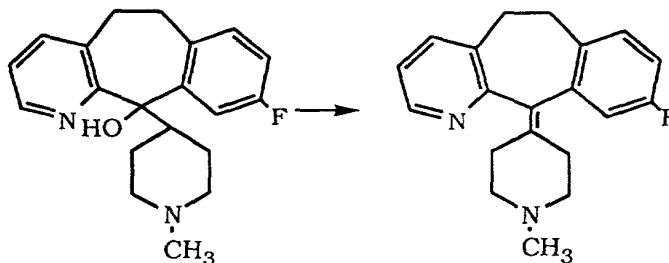
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D. 9-FLUORO-11-(1-METHYL-4-PIPERIDINYL)-6,11-DIHYDRO-5H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11-OL



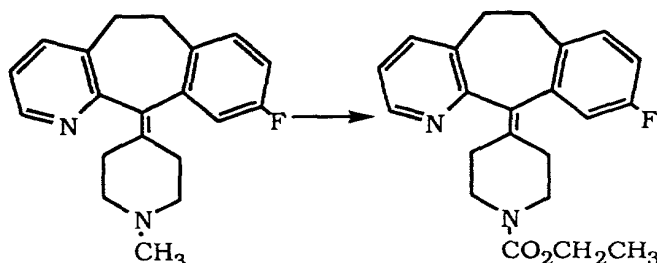
- Dissolve the title compound of Preparative Example 2C above (10.0 g, 44 mmol) in THF (100 mL) and add slowly to a cooled (-40°C) solution of the Grignard reagent prepared from N-methyl-4-chloropiperidine (57.9 mL, 88 mmol) and magnesium in THF (70 mL). Stir the mixture for about 1 hour while warming up to 0°C. Quench the reaction with NH<sub>4</sub>Cl solution and extract with EtOAc (2X). Wash the organic phase with brine and dry over Na<sub>2</sub>SO<sub>4</sub>, filter and remove the solvent. Purify the residue with flash chromatography and elute with MeOH (5%) in CHCl<sub>3</sub> to give the title compound as white granular crystals. (10.1 g, Yield 70%, m.p. 126-127°C after recrystallization from diisopropyl ether.)

E. 9-FLUORO-11-(1-METHYL-4-PIPERIDYLENE)-6,11-DIHYDRO-5H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDINE



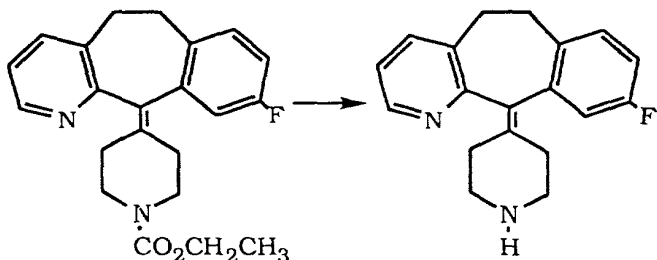
- Add the title compound of Preparative Example 2D above (7.3 g, 22.3 mmol) to a mixture of cooled H<sub>2</sub>SO<sub>4</sub> and CF<sub>3</sub>SO<sub>3</sub>H (1:1), (146 mL). Stir the reaction mixture for 0.5 hours at ice bath temperature and then at room temperature for 1.5 hours. Pour the reaction mixture onto ice and basify with NaOH (50%) solution. Extract the product with EtOAc (3X) and wash with brine. Dry the organic phase over Na<sub>2</sub>SO<sub>4</sub>, filter and remove the solvent to give a crude oil. Charcoal the oil and recrystallize from EtOAc and isopropyl ether to give the title compound. (5.6 g, Yield 82%, m.p. 134.5-135.5°C.).

F. 9-FLUORO-11-(1-ETHOXYCARBONYL-4-PIPERIDYLIDENE)-6,11-DIHYDRO-5H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDINE



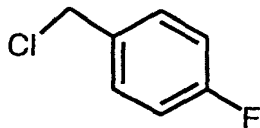
- 5 Stir a solution of the title compound of Preparative Example 2E above (5.0 g, 16.2 mmol) and Et<sub>3</sub>N (2.6 g, 26 mmol) in dry toluene (60 mL) at 80°C under an argon atmosphere, and add ethyl chloroformate (9.8 g, 90 mmol) via a syringe. Stir the reaction at this temperature for 30 minutes and at room temperature for one hour. Filter the reaction and remove the solvent. Pass the residue through a coarse SiO<sub>2</sub> column (60-200 mesh), and elute with CHCl<sub>3</sub> to yield the title compound as a white solid. (4.5 g, Yield 76%, m.p. 112-114°C after trituration with pentane).

G. 9-FLUORO-11-(4-PIPERIDYLIDENE)-6,11-DIHYDRO-5H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDINE

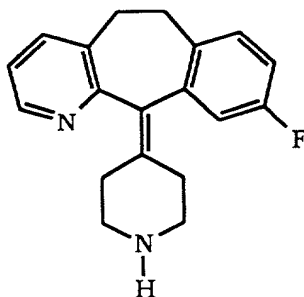


- 15 Reflux the title compound of Preparative Example 2F above (3.83 g, 10.4 mmol) with KOH (4.6 g) in 50 mL of EtOH/H<sub>2</sub>O (1:1) for 4 hours under an argon atmosphere. Pour the reaction mixture into a brine solution and extract with EtOAc (2X), dry over Na<sub>2</sub>SO<sub>4</sub> and filter. Remove the solvent to give the title compound (2.86 g, Yield 90%, m.p. 138-140°C.).

H. By employing the benzyl halide



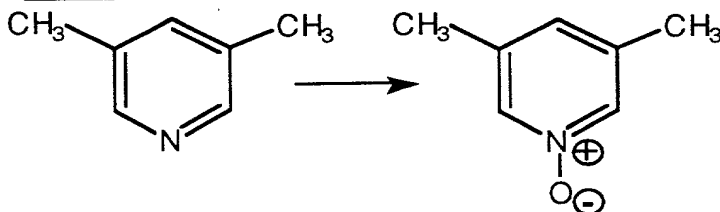
in place of 4-fluorobenzyl chloride in step 2A above, the product



is prepared (m.p. 138-140°C, triturated with pentane) by employing basically the same process as described in steps 2A-2G. Workup time is determined by either TLC or HPLC. In some instances purification of the product by chromatography is necessary.

### PREPARATIVE EXAMPLE 3

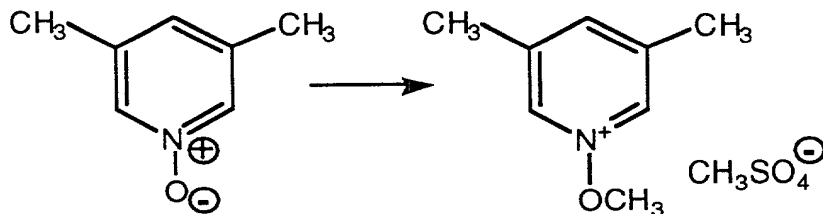
#### A. 3,5-DIMETHYLPYRIDINIUM N-OXIDE



A solution of 285 mL (1.31 mol) of 35% peracetic acid was slowly added to a stirred solution of 149 g (1.39 mol) of 3,5-dimethylpyridine during which the temperature rose to 85°C and was maintained at this temperature during addition. After the temperature of the mixture dropped to about 35°C the reaction was stored at 5°C overnight.

After partial removal of 185 ml of acetic acid via distillation under vacuum, the reaction was washed with NaHSO<sub>4</sub> solution and then neutralized with 10% NaOH solution to pH of about 7. The product was extracted with CH<sub>2</sub>Cl<sub>2</sub> to give the title compound as a white solid (yield 142 g, 83%).

#### B. 1-METHOXY-3,5-DIMETHYLPYRIDINIUM METHYL SULFATE

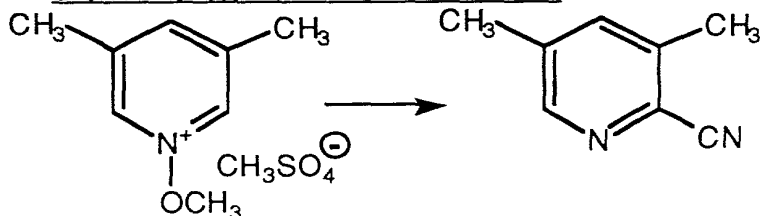


Dimethylsulfate (42.0 g, 0.33 mol) was slowly added to 41.0 g (0.33 mol) of 3,5-dimethylpyridinium N-oxide with mechanical stirring. The



mixture was then heated on a steam bath for 1 hr. Then vacuum was applied while cooling to give a brownish solid of the title compound in quantitative yield.

C. 2-CYANO-3,5-DIMETHYLPYRIDINE

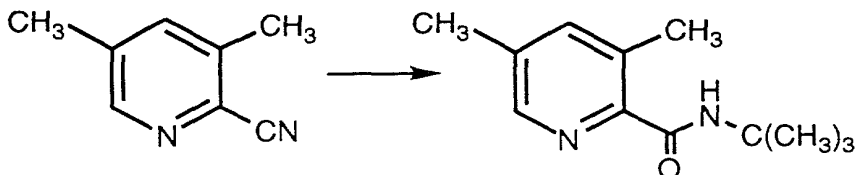


5

To a cooled (0°C) solution of sodium cyanide (49.0 g, 0.999 mol, 3.0 eq.) in 135 mL of water (air free) was dripped 1-methoxy-3,5-dimethyl pyridinium methyl sulfate (83.0g, 0.33 mol) in 100 mL water (air free) in 1.25 hr., keeping the temperature below 3°C. The reaction mixture was stored at about 3°C overnight. The mixture was filtered and washed with water to give 40g of the title compound. An analytical sample was recrystallized from isopropyl ether and pentane (4:1) (m.p.: 61-62°C).

10

D. N-(1,1-DIMETHYLETHYL)-3,5-DIMETHYL-2-PYRIDINE CARBOXAMIDE

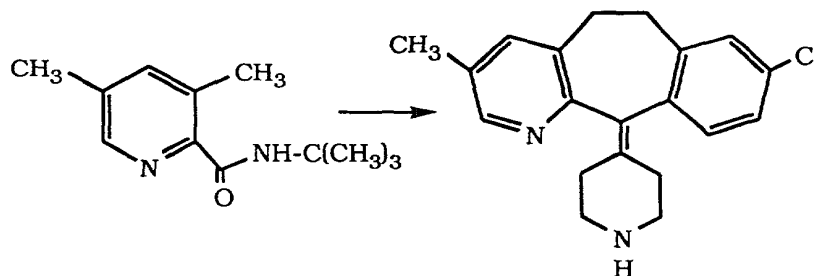


15

To a stirred solution of 20.3 g (0.153 mol) of 2-cyano-3,5-dimethylpyridine in 100 mL of 20 mL of conc. sulfuric acid within 10 minutes, followed by 20 mL of t-butanol over an additional 15 minutes. The solution was warmed at 75°C for 30 minutes after which it was cooled to room temperature and basified with 25% NaOH. The product was extracted 3X with EtOAc (600 mL), which was combined and washed 1X with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated in vacuo to give the title compound (31.26 g) as a yellowish oil.

20

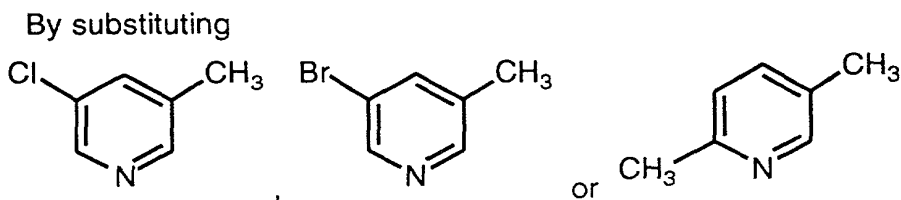
E. 8-CHLORO-3-METHYL-11-(4-PIPERIDYLIDENE)-6,11-DIHYDRO-5H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDINE



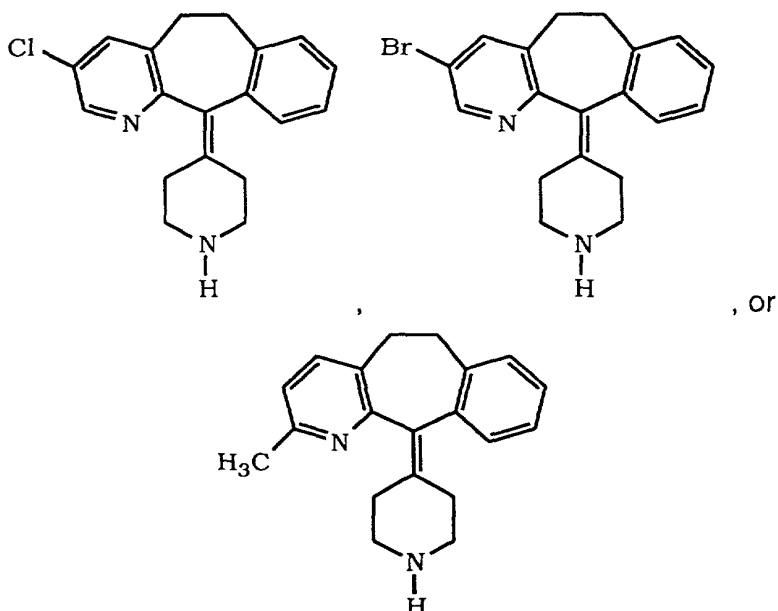
By substituting in step 1B above N-(1,1-dimethylethyl)-3,5-dimethyl-  
 5 2-pyridine carboxamide for N-(1,1-dimethylethyl)-3-methyl-2-pyridine  
 carboxamide and employing basically the same methods as steps B  
 through G of Preparative Example 1, one obtains 8-chloro-3-methyl-11-(4-  
 piperidylidene)-6,11-dihydro-5h-benzo[5,6]cyclohepta[1,2-b]pyridine.  
 Reaction times are determined by TLC or HPLC.

10

PREPARATIVE EXAMPLE 4



for 3,5-dimethylpyridine in Preparative Example 3 above and following  
 15 basically the same procedure (steps A-E), the compounds

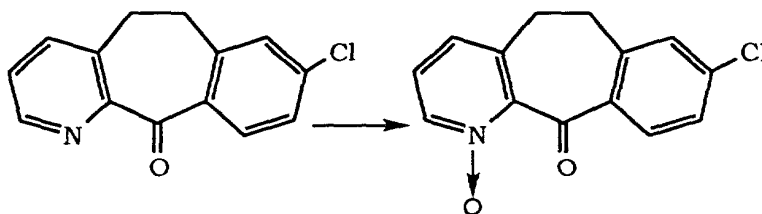


respectively, can be prepared. Note that the addition of the nitrile group to the pyridine in Step C of Preparative Example 3 can result in the formation of other undesirable isomers which can be removed via flash chromatography.

5

# PREPARATIVE EXAMPLE 5

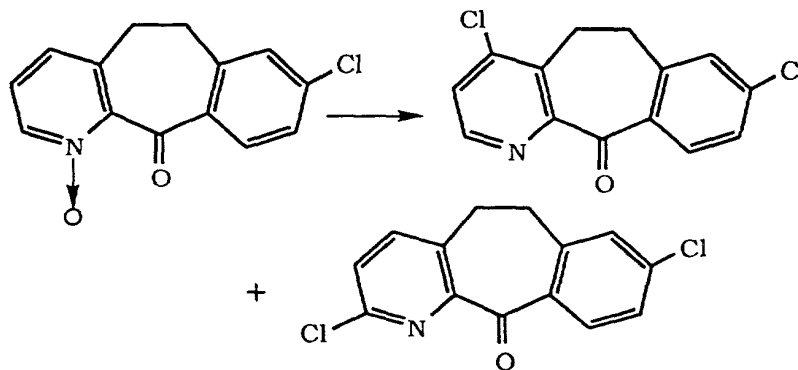
## A. 8-CHLORO-5,6-DIHYDRO-11H-BENZO[5,6]CYCLOHEPTA-[1,2-b]PYRIDIN-11-ONE N-OXIDE



10 To a mixture of 25.1 grams (0.103 mole) of 8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-one in 175 ml of dry CH<sub>2</sub>Cl<sub>2</sub> at 0°C under an argon atmosphere was added dropwise over 70 minutes a solution of 24.12 grams of 3-chloroperoxy-benzoic acid in 150 ml of CH<sub>2</sub>Cl<sub>2</sub>. After the addition the solution was stirred for 1/2 hour after which

15 the ice bath was removed. After two days the reaction was poured into 1.0 N aqueous NaOH and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic portions were combined, washed once with water, dried over MgSO<sub>4</sub>, filtered and concentrated in vacuo. The resultant product was triturated with isopropyl ether and filtered to provide 25.8 grams (96%) yield of the title compound.

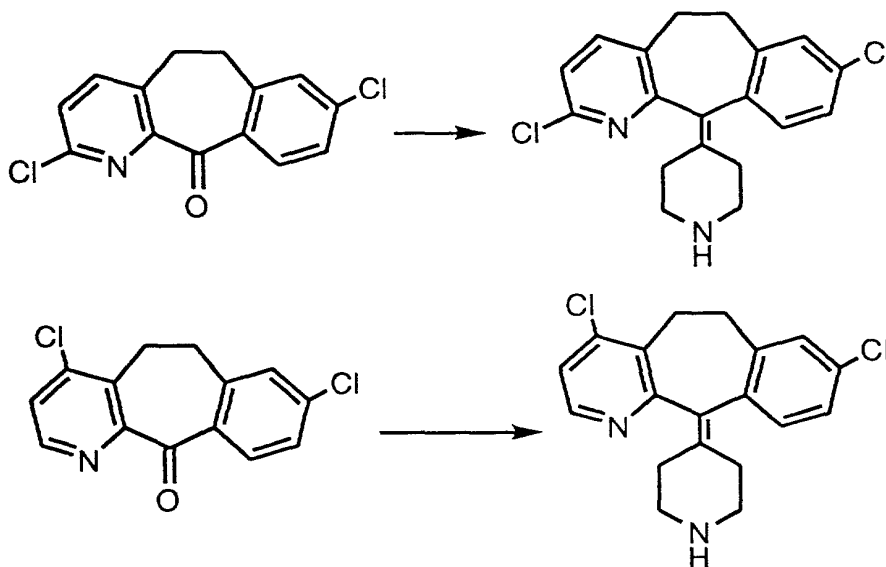
## 20 B. 2,8-DICHLORO-5,6-DIHYDRO-11H-BENZO[5,6]-CYCLOHEPTA[1,2-b]PYRIDIN-11-ONE AND 4,8-DICHLORO-5,6-DIHYDRO-11H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11-ONE



25 To a mixture of 29.13 grams (112.2 mmol) of the title compound from Preparative Example 5A above, in 40 ml of dry CH<sub>2</sub>Cl<sub>2</sub> at 0°C and under argon atmosphere was added 500 ml of 1.0 M SO<sub>2</sub>Cl<sub>2</sub> dropwise

over 1 hour. The ice bath was then removed and the reaction stirred at room temperature for 1 hr and then refluxed for seven hours. The mixture was poured into 1.0 N aqueous NaOH and extracted three times with CH<sub>2</sub>Cl<sub>2</sub>. The organic portions were combined, dried over MgSO<sub>4</sub>, filtered and concentrated in vacuo to yield a product which was purified and separated via flash chromatography to yield the two title compounds.

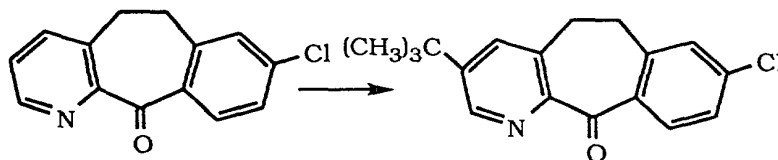
5 C. 4-(2,8-DICHLORO-5,6-DIHYDRO-11H-BENZO[5,6]-CYCLOHEPTA[1,2-b]PYRIDIN-11-YLIDENE)PIPERIDINE AND 4-(4,8-DICHLORO-5,6-DIHYDRO-11H-BENZO[5,6]CYCLOHEPTA-[1,2-b]-  
10 PYRIDIN-11-YLIDENE)PIPERIDINE



By following essentially the same procedure as that described in parts D-G of Preparative Example 2 above, the 2,8-dichloro and 4,8-dichloro products of Preparative Example 5B above were converted to the corresponding title compounds.

#### PREPARATIVE EXAMPLE 6

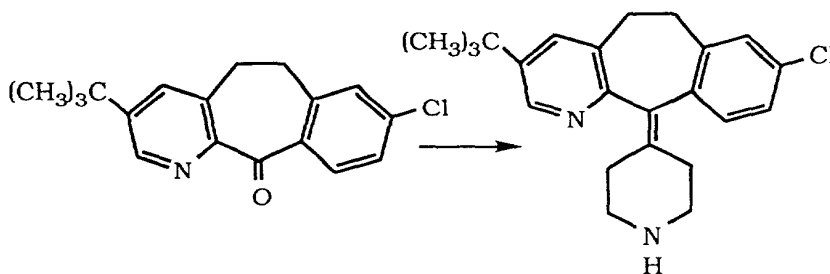
A. 3-(1,1-DIMETHYL-1-ETHYL)-8-CHLORO-5,6-DIHYDRO-11H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11-ONE



To a mixture of 20.05 grams (82.28 mmol) of 8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-one in 400 ml of dry THF at -72°C and under an atmosphere of nitrogen was added dropwise over 40

minutes 66.0 ml of 2.7 M t-butyl magnesium chloride in THF. The reaction mixture was slowly warmed to room temperature and stirred overnight. The mixture was then poured into 10% aqueous ammonium chloride and extracted four times with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic portions were dried over MgSO<sub>4</sub>, filtered, and concentrated in vacuo to give the title compound, along with 8-chloro-11-(1,1-dimethyl-1-ethyl)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ol. These compounds were separated via flash chromatography to give the title compound, which was recrystallized from isopropyl ether to give 4.37 grams (18%) of the title compound as a white solid.

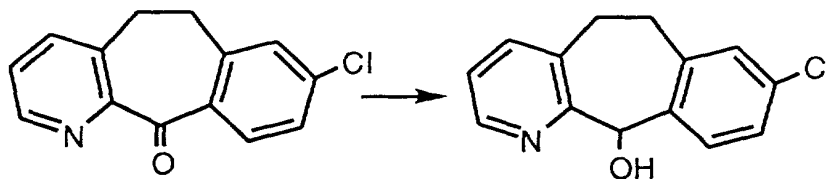
B. 4-[3-(1,1-DIMETHYL-1-ETHYL)-8-CHLORO-5,6-DIHYDRO-11H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11-YLIDENE]PIPERIDINE



By using the title compound of Part A above and applying essentially the same procedure described in parts D-G of Preparative Example 2 above, one can obtain the title compound.

PREPARATIVE EXAMPLE 7

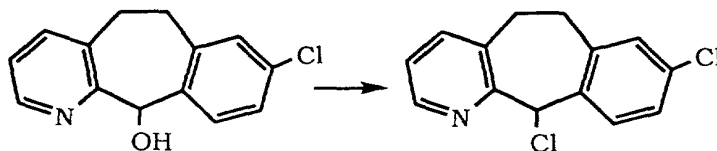
A. 8-CHLORO-6,11-DIHYDRO-11-HYDROXY-5H-BENZO[5,6]-CYCLOHEPTA[1,2-b]PYRIDINE



To a mixture of 25.03 g (103 mmol) of 8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-one in 200 mL of MeOH at room temperature and under a nitrogen atmosphere was added portionwise over a period of about 1 hour 4.82 g (124 mmol) of sodium borohydride. Occasional cooling with an ice bath was necessary at times during the addition in order to avoid excessive reflux. After 1.6 hours the mixture was poured into ice cold water and then extracted with EtOAc (3X). The combined organic portions were washed with brine, dried over MgSO<sub>4</sub>,

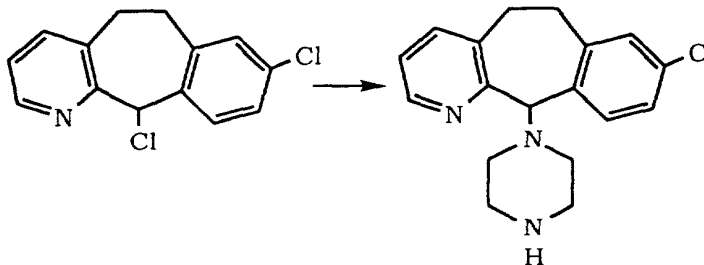
filtered, and concentrated in vacuo. The residue was recrystallized from hot isopropyl ether. The remaining filtrate was purified via flash chromatography (20% EtOAc in hexanes) to yield more product which solidified on standing. Both batches were combined to yield 20.41 g of the title compound as a white solid.

B. 8,11-DICHLORO-6,11-DIHYDRO-5H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDINE



To a mixture of 13.3 g (54 mmol) of 8-chloro-6,11-dihydro-11-hydroxy-5H-benzo[5,6]cyclohepta[1,2-b]pyridine in 290 mL of toluene at -15°C and under an atmosphere of nitrogen was added via syringe pump over a period of 1 hour 6.20 mL (85.7 mmol) of thionyl chloride. The extent of reaction was monitored by TLC (50% EtOAc in hexanes). When completed the mixture was poured into 300 mL of 1.0 N aqueous NaOH and extracted with EtOAc (5X). The combined organic portions were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was taken up in EtOAc, quickly filtered through basic alumina, and concentrated again to yield a product which was triturated with pentane to yield 10.22 g of the title compound as a tan solid.

C. 8-CHLORO-11-(1-PIPERAZINYL)-6,11-DIHYDRO-5H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDINE



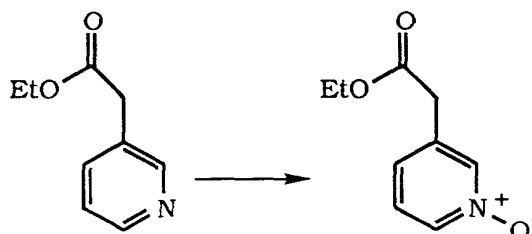
To a mixture of 10.0 g (37.9 mmol) of 8,11-dichloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine and 1.0 mL of Et<sub>3</sub>N in 200 mL of dry THF at room temperature and under a nitrogen atmosphere was added 33.0 g of piperazine. The mixture was stirred at room temperature for 22.5 hours and then refluxed for 5.5 hours. It was then cooled to room temperature, poured into 250 mL of 5% aqueous NaOH, and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3X). The combined organic portions were washed with

brine, dried over  $\text{MgSO}_4$ , filtered, and concentrated in vacuo. The residue was purified via flash chromatography (2→5% MeOH saturated with ammonia in  $\text{CH}_2\text{Cl}_2$ ) to yield the title compound as a glass.

5

PREPARATIVE EXAMPLE 8

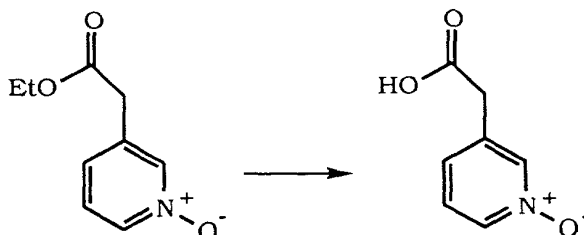
A. ETHYL 3-PYRIDYLACETIC ACID 1-N-OXIDE



Ethyl 3-pyridylacetic acid (10grams) (60.6 mmoles) was dissolved in dry  $\text{CH}_2\text{Cl}_2$  (120ml) and the solution was stirred at  $-18^\circ\text{C}$  for 30 minutes. MCPBA (31.34 grams) (181.6 mmoles) was added and the mixture was stirred at  $-18^\circ\text{C}$  for 1 hour and then at  $25^\circ\text{C}$  for 87 hours. The reaction mixture was diluted with  $\text{CH}_2\text{Cl}_2$  and washed with saturated aqueous sodium bicarbonate and then water. The  $\text{CH}_2\text{Cl}_2$  was then dried (magnesium sulphate), filtered and evaporated to dryness. The residue was chromatographed on silica gel using 3% (10% concentrated ammonium hydroxide in MeOH)- $\text{CH}_2\text{Cl}_2$  as the eluant to give the title compound (Yield: 8.45 grams, 77%,  $\text{MH}^+$  182).

15

B. 3-PYRIDYLACETIC ACID 1-N-OXIDE



3-Pyridylacetic acid (0.2747 grams) (1.5 mmoles) was dissolved in EtOH (200 proof) (1.22 ml.) and a 1M solution of LiOH in water (3.64 ml.) (3.0 mmoles) was added and the mixture was stirred at  $25^\circ\text{C}$  for 4 hours. 1N HCl (4.28 ml.) was added and the mixture was pumped down to dryness on a rotary evaporator to give the title compound (Yield: 0.2931 grams, 100%).

25

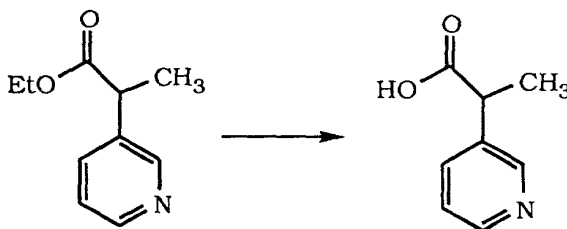
PREPARATIVE EXAMPLE 9

A. ETHYL  $\alpha$ -METHYL-3-PYRIDYLACETIC ACID.



To ethyl 3-pyridylacetic acid (10.86 grams) ( 65.7 mmoles) was  
5 added a 2.0M solution of lithium diisopropylamide in THF / heptane / ethyl  
benzene (32.87 ml.) (65.8 mmoles) at -30°C. The semi-solid mixture was  
agitated and sonicated for 1 hour. The mixture was allowed to remain at  
25°C for 1 hour, whereupon methyl iodide (4.09 ml.) (65.7 mmoles) was  
added. After 1 hour at 25°C the mixture was taken up in CH<sub>2</sub>Cl<sub>2</sub> and  
10 washed with saturated aqueous sodium bicarbonate and water. The  
CH<sub>2</sub>Cl<sub>2</sub> was dried (magnesium sulphate), filtered and evaporated to  
dryness. The residue was chromatographed on silica gel using 10%  
EtOAc in hexane as the eluant to give the title compound (Yield: 3.48  
grams, 30%, MH<sup>+</sup> 180).

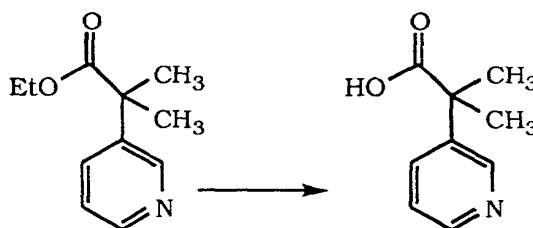
15 B.  $\alpha$ -METHYL-3-PYRIDYLACETIC ACID.



The title compound from Preparative Example 9A above (2.16  
grams) (12.05 mmoles) was dissolved in EtOH (10 ml.) and 1.0M LiOH in  
water (29.15 ml.) (29.2 mmoles) was added. The mixture was stirred at  
20 25°C for 4 hours, whereupon 1N HCl (34.27 ml.) (34.2 mmoles) was  
added and the solution was evaporated to dryness to give the title  
compound (Yield 2.33 grams, 100%).



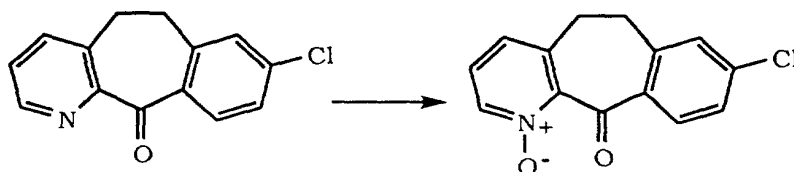
PREPARATIVE EXAMPLE 10  
 $\alpha,\alpha$ -DIMETHYL-3-PYRIDYLACETIC ACID.



5 Ethyl  $\alpha,\alpha$ -dimethyl -3-pyridylacetate (disclosed in EP Application 0 288 279, published October 26, 1988) (2.67 grams, 13.8 mmoles) was dissolved in EtOH (11.1 ml.) and a 1.0M LiOH in water (33.3 ml.) (33.4 mmoles) was added. The mixture was stirred at 25°C for 4 hours. 1N HCl (38.73 ml.) was added and after 5 minutes the mixture was evaporated to dryness to give the title compound (Yield: 100%).

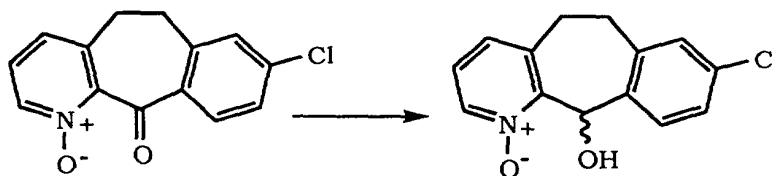
10

PREPARATIVE EXAMPLE 11  
A. 8-CHLORO-6,11-DIHYDRO-11-(1-PIPERAZINYL)-5H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDINE 1-N-OXIDE



15 To a mixture of 8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta- [1,2-b]pyridin-11-one (5 grams) (20.6 mmoles) in dry CH<sub>2</sub>Cl<sub>2</sub> (35 ml) was added dropwise MCPBA (4.7 grams) (27.3 mmoles) in dry CH<sub>2</sub>Cl<sub>2</sub> (75 ml) at 0-25°C over 1 hour. The mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> and washed with saturated aqueous sodium bicarbonate and water. The CH<sub>2</sub>Cl<sub>2</sub> was dried (magnesium sulphate), filtered and evaporated to dryness. The residue was chromatographed on silica gel using 1% (10% saturated ammonium hydroxide in MeOH)-CH<sub>2</sub>Cl<sub>2</sub> as the eluant to give the title compound (Yield: 2.81 grams, 53%, MH<sup>+</sup> 260).

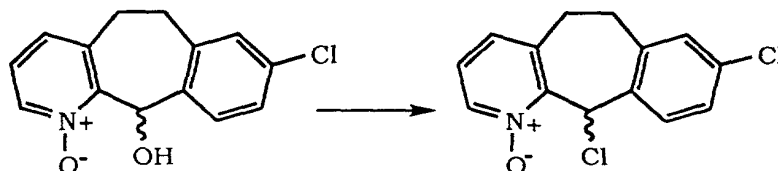
20 B. 8-CHLORO-6,11-DIHYDRO-5H-BENZO[5,6]CYCLOHEPTA-[1,2-b]PYRIDIN-11-OL 1-N-OXIDE



25

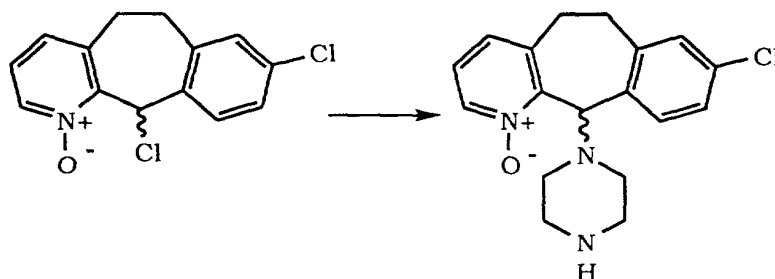
By using the title compound (8.6 grams) from Preparative Example 11A and reducing it by the procedure described in Preparative Example 7A above the title alcohol was obtained (Yield: 7.03 grams, 81%,  $MH^+$  262).

5 C. 8,11-DICHLORO-6,11-DIHYDRO-5H-BENZO[5,6]CYCLO-  
HEPTA[1,2-b]PYRIDINE 1-N-OXIDE



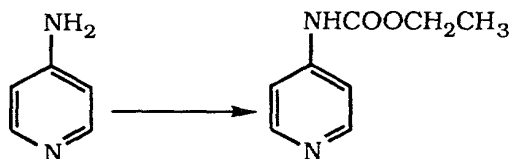
The title compound from Preparative Example 11B (6.2 grams) (23.7 mmoles) was reacted with thionyl chloride as described in  
10 Preparative Example 7B to give the title compound.

D. 8-CHLORO-6,11-DIHYDRO-11-(1-PIPERAZINYL)-5H-  
BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDINE 1-N-OXIDE



The title compound from Preparative Example 11C above was  
15 reacted with piperazine (9.9 grams) (115.0 mmoles) as described in  
Preparative Example 7C to give the title compound (Yield: 6.78 grams,  
87%,  $MH^+$  330).

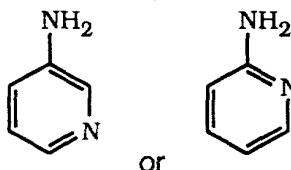
20 PREPARATIVE EXAMPLE 12  
4-ETHOXYCARBONYLAMINOPYRIDINE



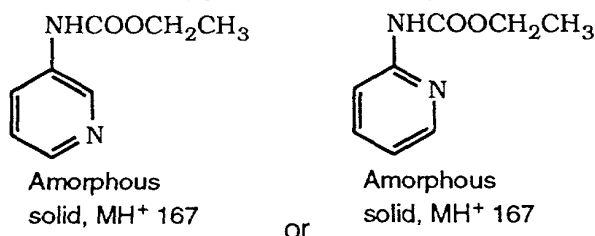
4-Aminopyridine (17.34 grams) (184.3) was dissolved in dry  
pyridine (217 ml.) and cooled to 0°C over 30 minutes. Ethyl chloroformate  
(17.2 ml.) (180.7 mmoles) was added and the solution was stirred at 0°C  
25 for 1 hour and then at 25°C for 40 hours. The mixture was diluted with  
 $CH_2Cl_2$  and washed with saturated aqueous  $NaHCO_3$  and water. The

$\text{CH}_2\text{Cl}_2$  was dried ( $\text{MgSO}_4$ ), filtered and evaporated to dryness. The residue was chromatographed on silica gel using 2%(10% saturated  $\text{NH}_4\text{OH}$  in  $\text{MeOH}$ )- $\text{CH}_2\text{Cl}_2$  to give the title compound (Yield: 10 grams, 33%,  $\text{M}^+$  166).

- 5 By using essentially the same procedure, with the exception that



was used instead of 4-aminopyridine, the compound

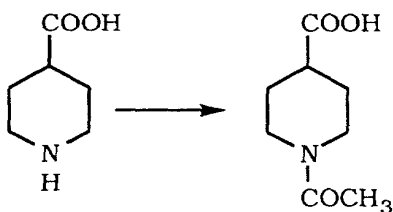


was obtained, respectively.

10

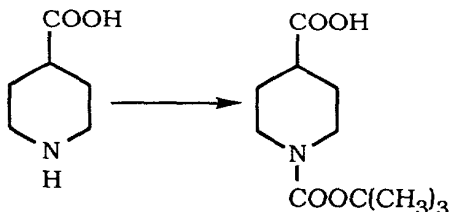
### PREPARATIVE EXAMPLE 13

#### A. N-ACETYLISONIPECOTIC ACID



- 15 Isonipecotic acid (10 grams) (77.5 mmoles) and acetic anhydride (23.7 grams) (232.5 mmoles) were dissolved in  $\text{MeOH}$  (100 ml.) and the mixture was stirred at  $25^\circ\text{C}$  for 24 hours. The mixture was evaporated to dryness and the residue was azeotroped with toluene to give the title compound (Yield: 12.8 grams, 97%,  $\text{MH}^+$  172).

#### B. 1-N-tert-BUTOXYCARBONYLISONIPECOTIC ACID



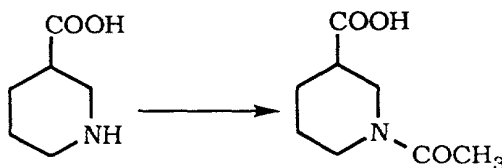
20

Isonipecotic acid (20 grams) (155.0 mmoles) was dissolved in  $\text{THF}$ -water (1:1) (400 ml) and  $\text{NaOH}$  (6.2 grams) (155.0 mmoles) and di-tert-

butyldicarbonate (37.2 grams) (170.5 mmoles) were added. The mixture was stirred at 25°C for 72 hours. The solution was then eluted through a bed of washed BioRad 50WX4 (RSO3H resin) (150 ml bed) and the resin was eluted with a 1:1 mixture of THF and water. The eluate was  
5 evaporated to dryness to give the title compound (Yield: 33.78 grams, 90%).

PREPARATIVE EXAMPLE 14

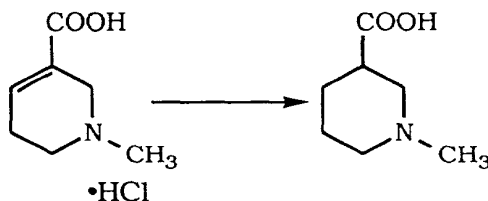
1-N-ACETYLNIEPECOTIC ACID



Nipepic acid (3.87 grams) (30.0 mmoles) was reacted with acetic anhydride (9.17 grams) (90 mmoles) as described in Preparative Example 13A to give the title compound (Yield: 5.0 grams, 97%,  $MH^+$  172).

PREPARATIVE EXAMPLE 15

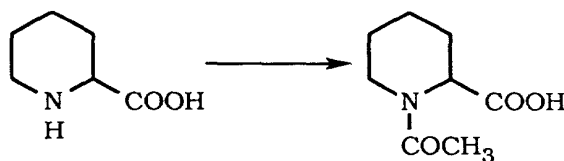
1-N-METHYLNIEPECOTIC ACID



Arecaidine hydrochloride (4 grams) (22.6 mmoles) was hydrogenated in water (100 ml) using 10% Pd-C at 40 psi at 25°C for 24  
20 hours. The catalyst was filtered off and washed with water. The aqueous solution was shaken with BioRad AG1X8 resin ( $OH^-$  form) (23 ml bed) and after 5 minutes the resin was filtered off and washed with water. The aqueous solution was evaporated to give the title compound (Yield: 2.95  
25 grams, 92%).

PREPARATIVE EXAMPLE 16

1-N-ACETYL D,L-PIPECOLINIC ACID

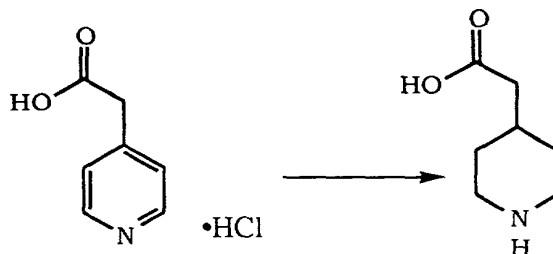


D,L-Pipecolic acid (10 grams) (77.5 mmoles) and acetic anhydride (23.7 grams) (232.5 mmoles) were reacted as described in Preparative Example 13A above to give the title compound (Yield: 12.94 grams, 98%,  $MH^+$  172).

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PREPARATIVE EXAMPLE 17

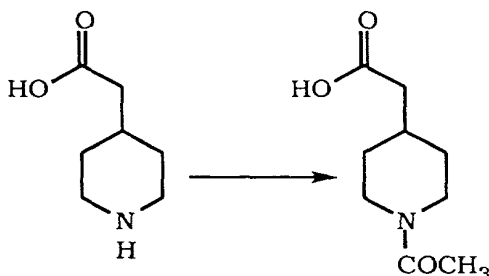
A. PIPERIDINE-4-ACETIC ACID



4-Pyridylacetic acid (7 grams) (40.4 mmoles) was hydrogenated as described in Preparative Example 15 to give the title compound (Yield: 5.2 grams, 90%,  $MH^+$  144).

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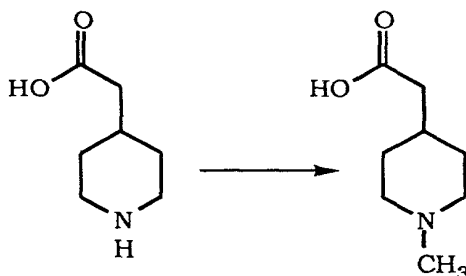
B. 1-N-ACETYL-4-PIPERIDINYLACETIC ACID



4-Piperidinylacetic acid (5 grams) (35.0 mmoles) was reacted with acetic anhydride (10.7 grams) (105.0 mmoles) as described in Preparative Example 13A to give the title compound (Yield: 6.4 grams, 99%,  $MH^+$  185).

15

C. 1-N-METHYL-4-PIPERIDINYLACETIC ACID

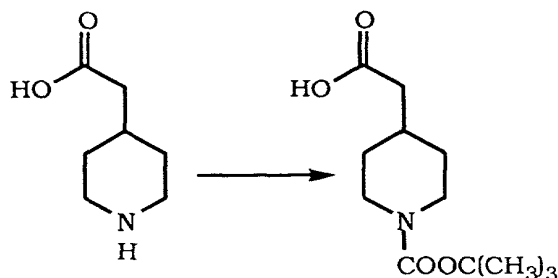


4-Piperidinylacetic acid (4 grams) (28.0 mmoles) from Preparative Example 17A was dissolved in water (50 ml) and 37% formalin (2.72 ml) (33.6 mmoles) was added. The mixture was hydrogenated over 10% Pd-

20

C at 55psi at 25°C for 68 hours. The catalyst was filtered off and washed with water. The combined filtrates were evaporated to dryness to give the title compound (  $MH^+$ 158).

D. 1-N-tert-BUTOXYCARBONYLPIPERIDINYL-4-ACETIC ACID



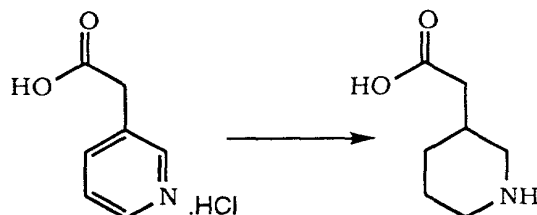
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4-Piperidinylacetic acid (41.24 grams) (288.4 mmoles) from Preparative Example 17A was reacted with di-tert-butylidicarbonate (69.14 grams) (317.3 mmoles) and NaOH (11.52 grams) (288.4 mmoles) as described in Preparative Example 13B above to give the title compound (Yield: 53.0 grams, 76%).

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PREPARATIVE EXAMPLE 18

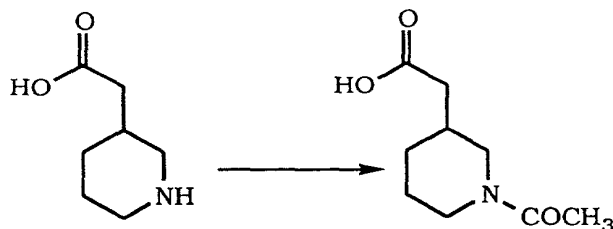
A. 3-PIPERIDINYLACETIC ACID



15

3-Pyridylacetic acid hydrochloride (13 grams) (74.9 mmoles) was hydrogenated as described in Preparative Example 15 to give a mixture of unreacted 3-pyridylacetic acid and the title compound (76:24) (8.63 grams,  $MH^+$  144).

B. 1-N-ACETYL-3-PIPERIDINYLACETIC ACID

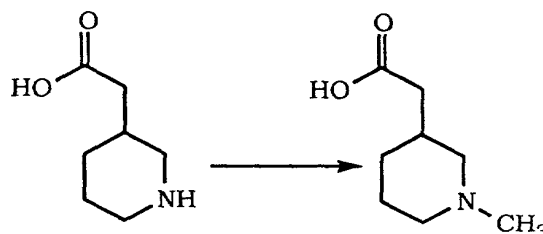


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The mixture of compounds from Preparative Example 18A (8.56 grams) were reacted with acetic anhydride (8.56 grams) as described in Preparative Example 13A and the crude mixture of products was taken up

in MeOH (60 ml) and passed over a bed of BioRad AG50WX4 resin (RSO<sub>3</sub>H) and the latter was eluted with MeOH. The eluates were evaporated to dryness to give the title compound (Yield: 1.23 grams, MH<sup>+</sup> 186).

5 C. 1-N-METHYL-3-PIPERIDINYLACETIC ACID



The mixture of compounds from Preparative Example 18A (4 grams) and 37% formalin (2.72 ml.) were hydrogenated as described in Preparative Example 17C to give the title compound (MH<sup>+</sup> 158).

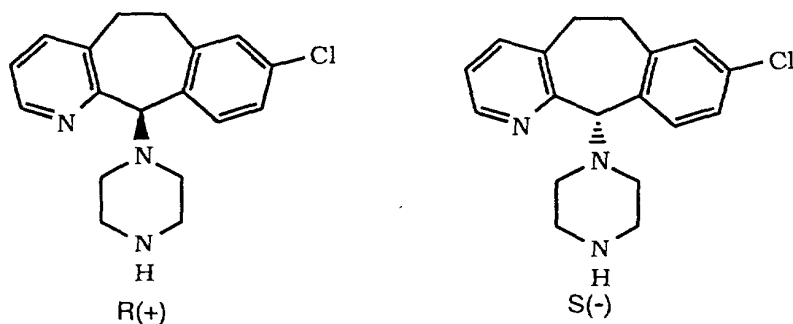
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PREPARATIVE EXAMPLE 19

PREPARATION OF THE R(+) AND S(-) DIASTEREOMERS

The racemic 8-chloro-11-(1-piperazinyl)-6,11-dihydro-5H-benzo-[5,6]cyclohepta[1,2-b]pyridine prepared in Preparative Example 7C above was resolved by the method described in Preparative Example 15 A-C, pages 116-118, of WO 92/00293, published January 9, 1992, to give the R(+) and S(-) diastereoisomers:

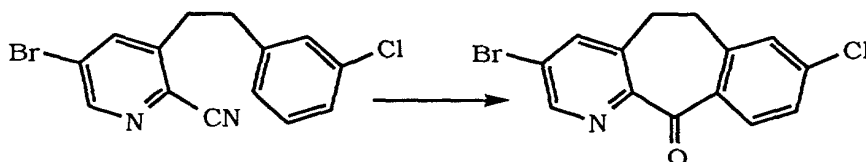
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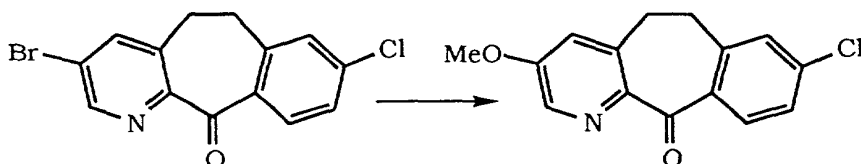
PREPARATIVE EXAMPLE 20

A. 3-BROMO-8-CHLORO-5,6-DIHYDRO-11H-BENZO[5,6]-CYCLOHEPTA[1,2-b]PYRIDIN-11-ONE



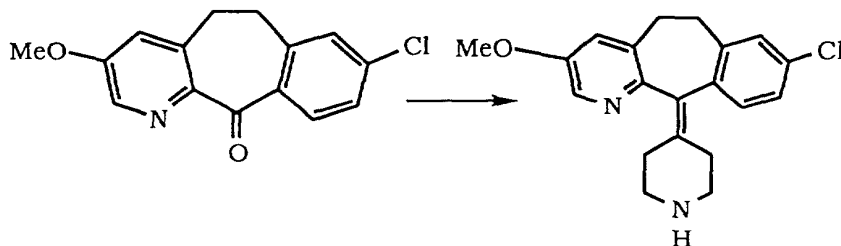
Cyclize 3-[2-(3-chlorophenyl)ethyl]-4-bromo-2-pyridine carbonitrile (10.7g, 32.8 mmol) in triflic acid (82 mL) at 60°C for 2 hours and then at room temperature for 2 hours. Add 80 mL of 5N HCl carefully, then reflux in an oil bath (120°C) for 30 minutes. Cool the solution and pour into ice and basify with 25% NaOH solution. Extract the product with CH<sub>2</sub>Cl<sub>2</sub> and wash with brine. Dry the organic layer with Na<sub>2</sub>SO<sub>4</sub>, filter and remove the solvent to give crude product (10.4g). Purify the crude product with flash chromatography on silica gel and elute with 15% EtOAc-hexane to give the title compound as a white solid (9g, 27.95 mmol, Yield 85.2% MH<sup>+</sup> 322).

B. 8-CHLORO-3-METHOXY-5,6-DIHYDRO-11H-BENZO[5,6]-CYCLOHEPTA[1,2-b]PYRIDIN-11-ONE



Dissolve the title compound of Preparative Example 20A (2.37g, 7.4 mmol) in dry MeOH and add Na metal (3.37g, 180 mmol). the reaction is stirred overnight at room temperature. Reflux the reaction for 3 hours, cool to room temperature and extract with CH<sub>2</sub>Cl<sub>2</sub>-water. Dry the CH<sub>2</sub>Cl<sub>2</sub> fraction and chromatograph on silica gel eluting with 50% EtOAc-hexanes to give the title compound as a light yellow solid (1.5g, Yield 72% MH<sup>+</sup> 274).

C. 8-CHLORO-3-METHOXY-11-(4-PIPERIDYLIDENE)-6,11-DIHYDRO-5H-BENZO[5,6]-CYCLOHEPTA[1,2-b]PYRIDINE

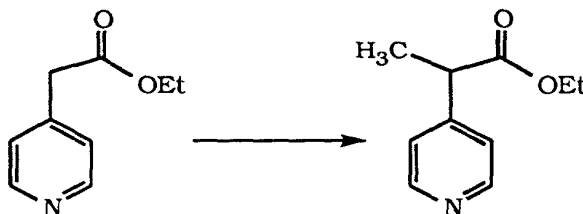


By substituting in Preparative Example 2 step D, 8-chloro-3-methoxy-5,6-dihydro-11H-benzo[5,6]-cyclohepta[1,2-b]pyridin-11-one for 9-fluoro-5,6-dihydro-11H-benzo[5,6]-cyclohepta[1,2-b]pyridin-11-one and employing basically the same methods as steps D through H of Preparative Example 2, one obtains 8-chloro-3-methoxy-11-(4-piperidylidene)-6,11-dihydro-5H-benzo[5,6]-cyclohepta[1,2-b]pyridine as a white solid (MH<sup>+</sup> 340).



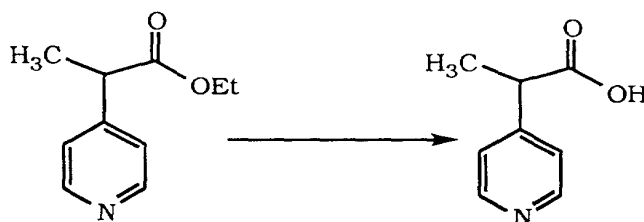
PREPARATIVE EXAMPLE 25

A. ETHYL  $\alpha$ -METHYL-4-PYRIDYL ACETIC ACID



To dry THF at  $-78^{\circ}\text{C}$  was added diisopropylamine (5.05g 48 mmol, 7mL) and then *n*-butyl lithium. The reaction mixture was stirred for 0.5 h and then ethyl 4-pyridyl acetic acid (7.85g, 46 mmol) was added, and after stirring for 0.5 h at that  $-78^{\circ}\text{C}$  the reaction temperature was raised to room temperature. DMF (20 mL) was added and the reaction mixture cooled to  $-78^{\circ}\text{C}$  again. Methyl iodide (7.07g, 50.2 mmol, 3.15 mL) was added and the reaction mixture stirred at that temperature for 1h and then at room temperature overnight. All the volatiles were then stripped off and the reaction mixture was partitioned between water- $\text{CH}_2\text{Cl}_2$ . The aqueous phase was washed twice with  $\text{CH}_2\text{Cl}_2$ . The combined  $\text{CH}_2\text{Cl}_2$  phases were dried and evaporated. The crude product was chromatographed on silica gel eluting with 80% EtOAc hexane to give the title compound (7.88g,  $\text{MH}^+$  179).

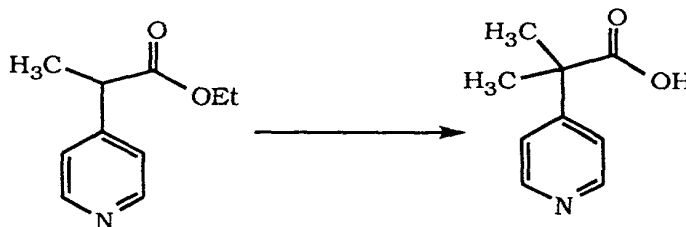
B.  $\alpha$ -METHYL-4-PYRIDYL ACETIC ACID



The compound from Preparative Example 25A was hydrolysed in a similar manner to Preparative Example 9B to give the title compound ( $\text{MH}^+$  152).

PREPARATIVE EXAMPLE 26

A.-B.  $\alpha,\alpha$ -DIMETHYL-4-PYRIDYL ACETIC ACID

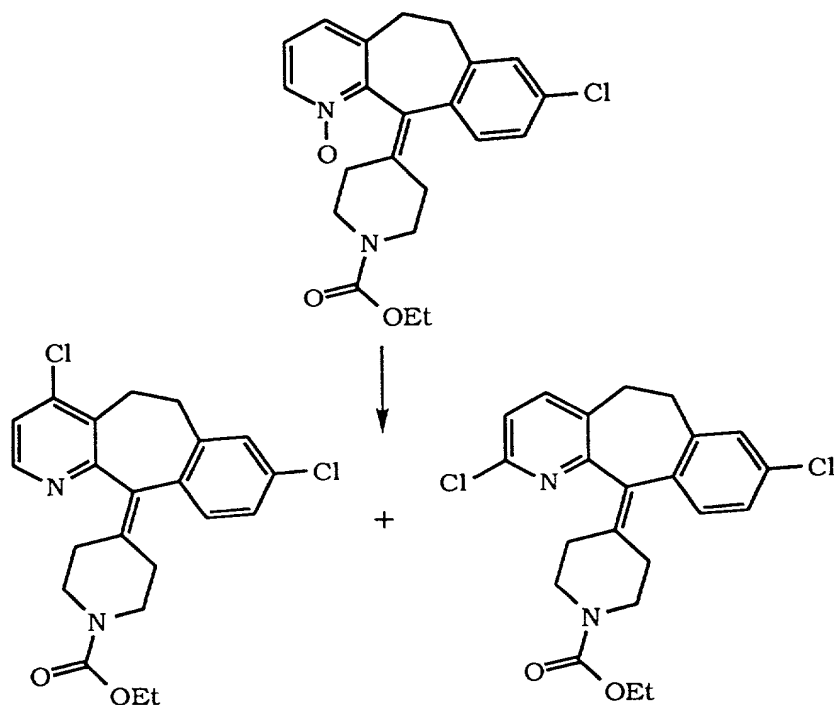


By essentially the same procedure as set forth in Preparative Example 10A-B, but using ethyl  $\alpha$ -methyl-4-pyridylacetic acid (from Preparative Example 25) instead of ethyl pyridyl acetic acid the title compound was obtained as an oil ( $MH^+$  166).

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PREPARATIVE EXAMPLE 27

ETHYL 4-[4,8-DICHLORO-5,6-DIHYDRO-11H-BENZO[5,6]CYCLO-  
HEPTA[1,2-b]PYRIDIN-11-YLIDENE]-1-PIPERIDINECARBOXYLATE and  
ETHYL 4-[2,8-DICHLORO-5,6-DIHYDRO-11H-  
10 BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11-YLIDENE]-1-PIPERIDINE-  
CARBOXYLATE



To phosphorous oxychloride (256 mL) stirring at reflux was added dropwise a solution of the title compound (109 grams) from Example 231A dissolved in  $CHCl_3$  (850 mL). After stirring the resulting solution for an additional 20 minutes at reflux, the reaction mixture was cooled to room temperature and the chloroform removed *in vacuo*. The resulting solution was cooled in an ice-water bath and to it was slowly added 1N aqueous NaOH (850 mL) followed by 50% aqueous NaOH until the resulting mixture was slightly basic. Extraction with EtOAc, drying of the organic phase over anhydrous  $MgSO_4$ , concentration *in vacuo*, and purification by flash column chromatography provided the 4,8-dichloro product (27

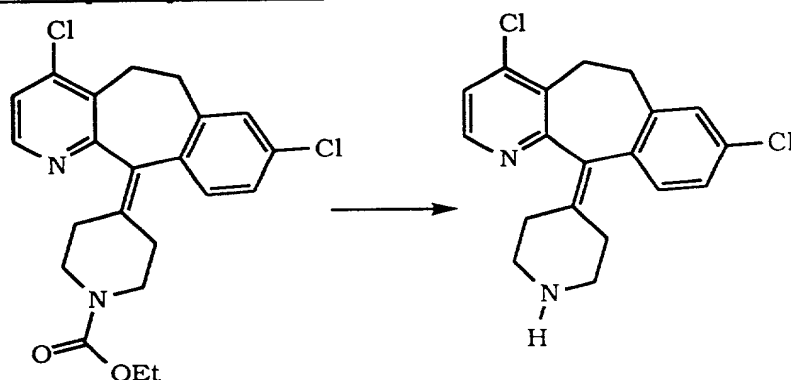
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grams, 23% yield, mp 141.6-145.6 °C) and the 2,8-dichloro product (9 grams, 8% yield, 176.5-177.9 °C).

PREPARATIVE EXAMPLE 28

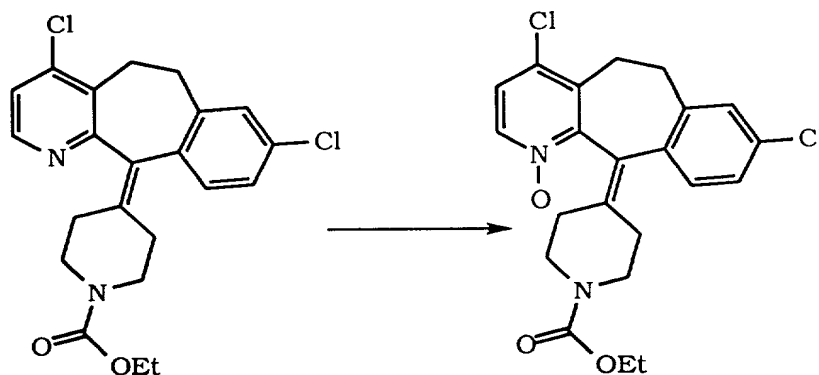
5      4,8-DICHLORO-11-(4-PIPERIDYLIDENE)-6,11-5H-BENZO[5.6]-CYCLOHEPTA[1.2-b]PYRIDINE



A solution of the 4,8-dichloro compound from Preparative Example 27 (2.6 grams) dissolved in absolute EtOH (50 mL) and concentrated HCl (100 mL) was stirred at reflux for 48 hours. The reaction mixture was cooled in an ice-water bath and was made basic by addition of solid KOH. Concentration *in vacuo* afforded a solid which was diluted with CH<sub>2</sub>Cl<sub>2</sub> and water. The organic phase was dried over anhydrous MgSO<sub>4</sub> and concentrated *in vacuo* to provide the title compound (2.0 grams, 93% yield, mp = 181.1-183.2°C).

PREPARATIVE EXAMPLE 29

20      ETHYL 4-[4,8-DICHLORO-5,6-DIHYDRO-11H-BENZO[5.6]CYCLOHEPTA[1.2-b]PYRIDIN-11-YLIDENE]-1-PIPERIDINE CARBOXYLATE, N-OXIDE

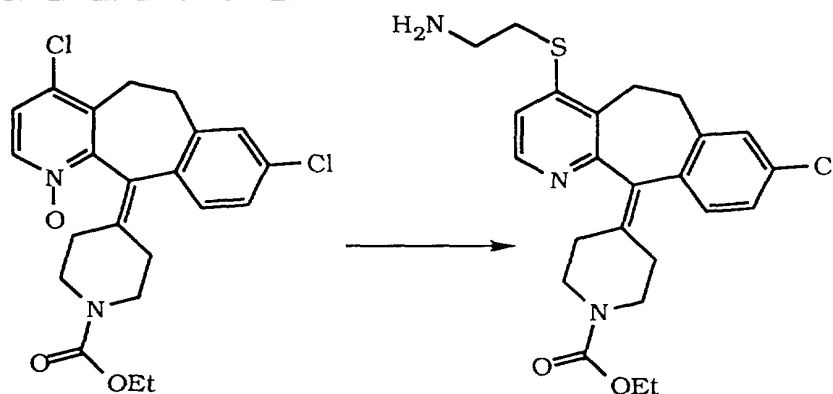


To a cooled (0°C) solution of the 4,8-dichloro compound from Preparative Example 27 (9.5 grams) dissolved in CH<sub>2</sub>Cl<sub>2</sub> (300 mL) under

N<sub>2</sub> was added dropwise a solution of MCPBA (6.8 grams) dissolved in EtOAc (200 mL). The resulting mixture was washed with 1N aqueous NaOH, dried over anhydrous MgSO<sub>4</sub> and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel) using 100% EtOAc then 10% MeOH-CH<sub>2</sub>Cl<sub>2</sub> to afford the title compound (4.9 grams, 50%, MH<sup>+</sup> 433).

PREPARATIVE EXAMPLE 30

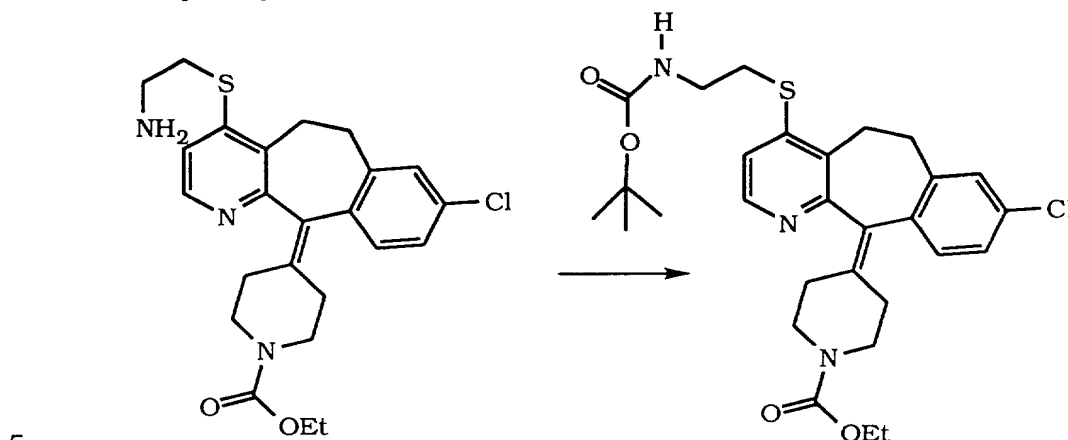
ETHYL 4-[4-(2-AMINOETHYLTHIO)-8-CHLORO-5,6-DIHYDRO-11H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11-YLIDENE]-1-PIPERIDINE CARBOXYLATE



A mixture of the title compound from Preparative Example 29 (0.53 grams), 2-aminoethanethiol hydrochloride (0.74 grams) and absolute EtOH (15 mL) was stirred at reflux for 48 hours. The mixture was cooled to 25°C, diluted with CH<sub>2</sub>Cl<sub>2</sub> and washed with 1N aqueous NaOH. The organic phase was dried over anhydrous MgSO<sub>4</sub> and concentrated *in vacuo* to provide the title compound (0.5 grams, 88%, MH<sup>+</sup> 458).

PREPARATIVE EXAMPLE 31

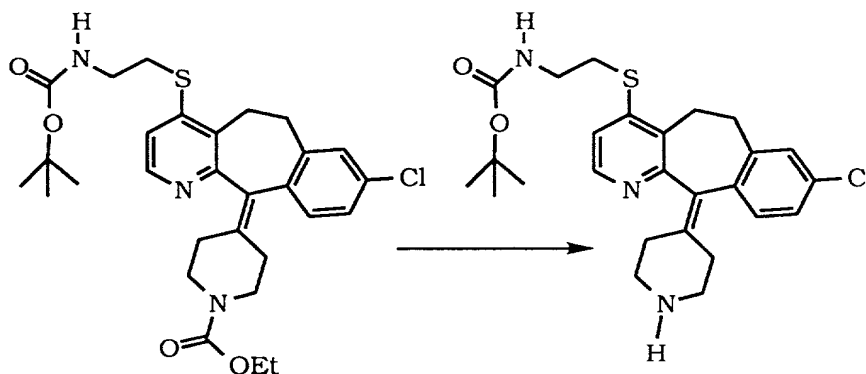
1,1-DIMETHYLETHYL [2-[[8-CHLORO-6,11-DIHYDRO-11-(1-ETHOXYCARBONYL)-4-PIPERIDINYLIDENE]-5H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-4-YL]THIO]ETHYL]CARBAMATE



To the title compound from Preparative Example 30 (0.33 grams) dissolved in  $\text{CH}_2\text{Cl}_2$  (60 mL) was added di-*tert*-butyldicarbonate (0.17 grams). The solution was stirred at  $25^\circ\text{C}$  under  $\text{N}_2$  overnight. An additional 0.1 grams of di-*tert*-butyldicarbonate was added and after 4 hours the reaction mixture was diluted with  $\text{CH}_2\text{Cl}_2$ , washed with 1N aqueous NaOH and concentrated *in vacuo* to afford the title compound (0.5 grams, 100%,  $\text{MH}^+$  558).

PREPARATIVE EXAMPLE 32

15 1,1-DIMETHYLETHYL [2-[[8-CHLORO-6,11-DIHYDRO-11-[4-PIPERIDINYLIDENE]-5H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-4-YL]THIO]ETHYL]CARBAMATE

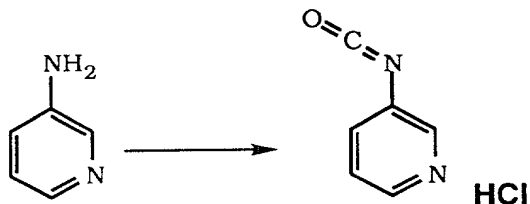


20 To the title compound from Preparative Example 31 (0.22 grams) dissolved in absolute EtOH (5 mL) was added water (5 mL) and solid KOH (0.33 grams). The solution was stirred at reflux for 4 days, then cooled to

25°C, diluted with CH<sub>2</sub>Cl<sub>2</sub> and washed with water. The organic phase was concentrated *in vacuo* and the residue purified by flash column chromatography (silica gel) using 5% MeOH-CH<sub>2</sub>Cl<sub>2</sub> saturated with NH<sub>4</sub>OH to afford the title compound (0.04 grams, 19%, MH<sup>+</sup> 486).

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PREPARATIVE EXAMPLE 33  
3-PYRIDYLISOCYANATE, HYDROCHLORIDE

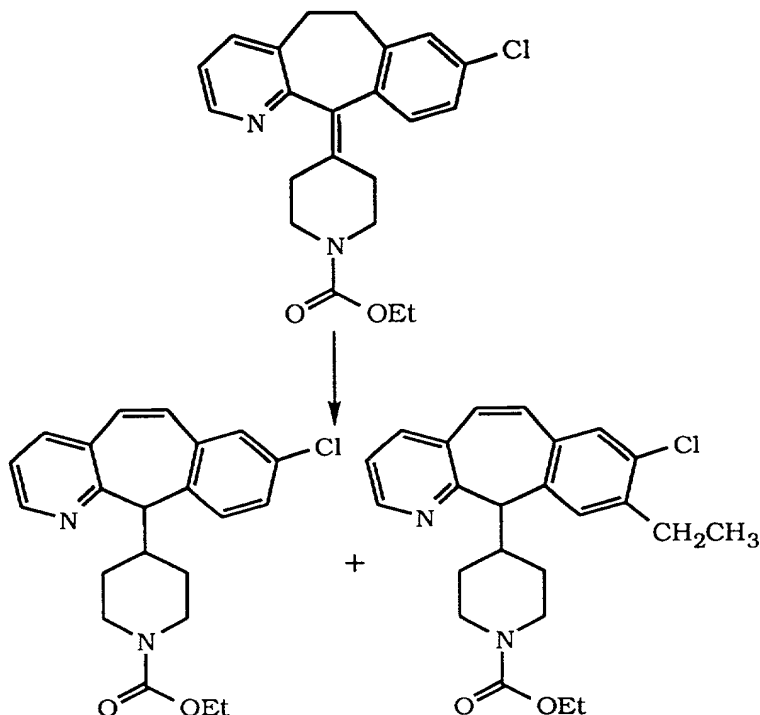


- 10 A 1.93 solution of phosgene in toluene (20%) (584 mL) was diluted with dry CH<sub>2</sub>Cl<sub>2</sub> (1 L) and the mixture was stirred at 0°C under nitrogen atmosphere. A solution of 3-aminopyridine (21.1 grams) and dry pyridine (19 mL) dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (600 mL) was added dropwise to the stirred solution at 0°C over a period of 5.5 hours. The mixture was stirred at 0-25°C for an additional 48 hours. A stream of nitrogen was passed
- 15 through the solution to remove most of the phosgene and the solution was then evaporated until almost all of the solvent was removed to give the title compound which was then taken up in dry pyridine (850 mL) to give a stock solution of the title compound.

PREPARATIVE EXAMPLE 34

A. 8-CHLORO-11-(1-ETHOXYCARBONYL-4-PIPERIDINYL)-  
11H-BENZO[5,6]CYCLOHEPTA(1,2-b)PYRIDINE

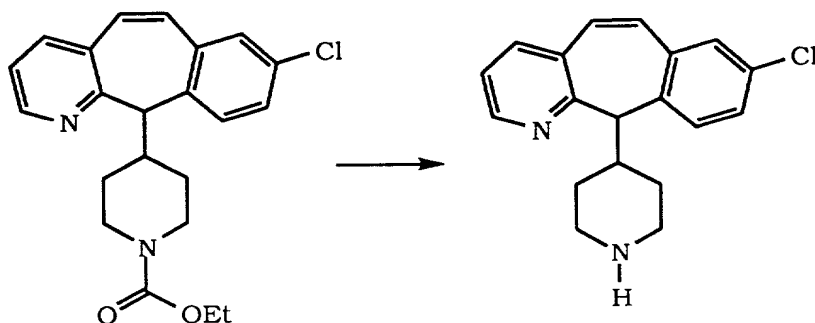
B. 8-CHLORO-11-(1-ETHOXYCARBONYL-4-PIPERIDINYL)-9-  
5 ETHYL-11H-BENZO[5,6]CYCLOHEPTA(1,2-b)PYRIDINE



The title compound of Preparative Example 1F above (51.15 grams, 0.1336 mole) was dissolved in trifluoromethanesulfonic acid (170 mL). The dark mixture was heated to reflux for 70h. The solution was cooled to room temperature and was then poured into 800 mL of an ice/water slurry and the resulting mixture stirred. Concentrated NH<sub>4</sub>OH solution (175 mL) was added to the mixture in small portions so that the temperature of the mixture was below 20°C. The resulting basic mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The CH<sub>2</sub>Cl<sub>2</sub> extract was washed with brine and was then evaporated to give a brown residue. This residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (750 mL) and the solution cooled to 0°C. Ethyl chloroformate (14.8 grams, 0.136 mole) was added over 5 minutes and the resulting mixture stirred at 0°C for 15 minutes. Saturated NaHCO<sub>3</sub> solution (150 mL) was added and the cooling bath was removed. The resulting biphasic mixture was stirred rapidly for 3h. The layers were separated and the CH<sub>2</sub>Cl<sub>2</sub> layer was filtered through silica gel. The filtrate was evaporated to dryness and the residue chromatographed on silica gel

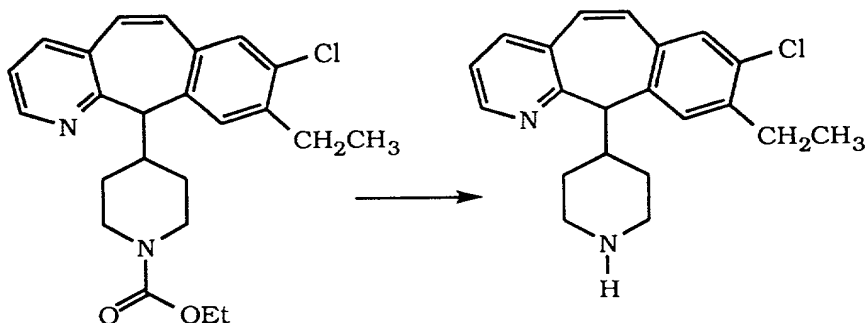
using a gradient of hexane-CH<sub>2</sub>Cl<sub>2</sub>-acetone 16:2.5:1.5 to hexane-CH<sub>2</sub>Cl<sub>2</sub>-acetone 28:7.5:4.5 as eluent to give title compound A (25.02g 49% MH<sup>+</sup> 383) and title compound B (4.85g, 9%, MH<sup>+</sup> 411).

5 C. 8-CHLORO-11-(4-PIPERIDINYL)-11H-BENZO[5.6]CYCLO-  
HEPTA(1,2-b)PYRIDINE



Hydrolyze the title compound of Preparative Example 34A by dissolving in 50% aqueous H<sub>2</sub>SO<sub>4</sub> (v/v) and heating to 90° to 100°C for 16 h. The cooled acidic mixture was neutralized with 25% NaOH solution (w/v). The resulting mixture was extracted with EtOAc and the EtOAc extract was dried with Na<sub>2</sub>SO<sub>4</sub>. Filtration and evaporation of the EtOAc afforded the title compound (MH<sup>+</sup> 311).

15 PREPARATIVE EXAMPLE 35  
8-CHLORO-9-ETHYL-11-(4-PIPERIDINYL)-11H-BENZO-  
[5.6]CYCLOHEPTA[1,2-b]PYRIDINE

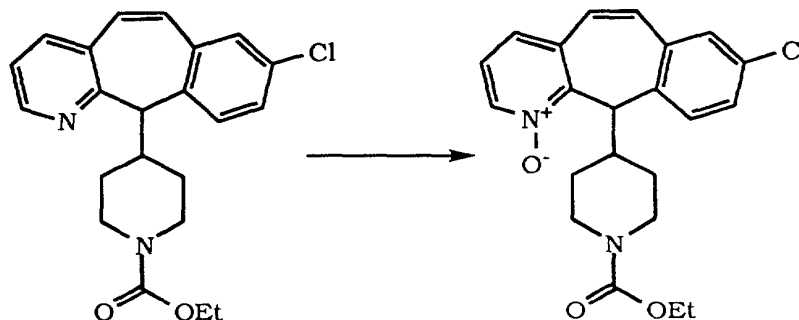


Hydrolyze the title compound of Preparative Example 34B following the procedure described in Preparative Example 34C to provide the title compound. Decomposes between 205.7-215.4°C, heating 2-3°C per minute.



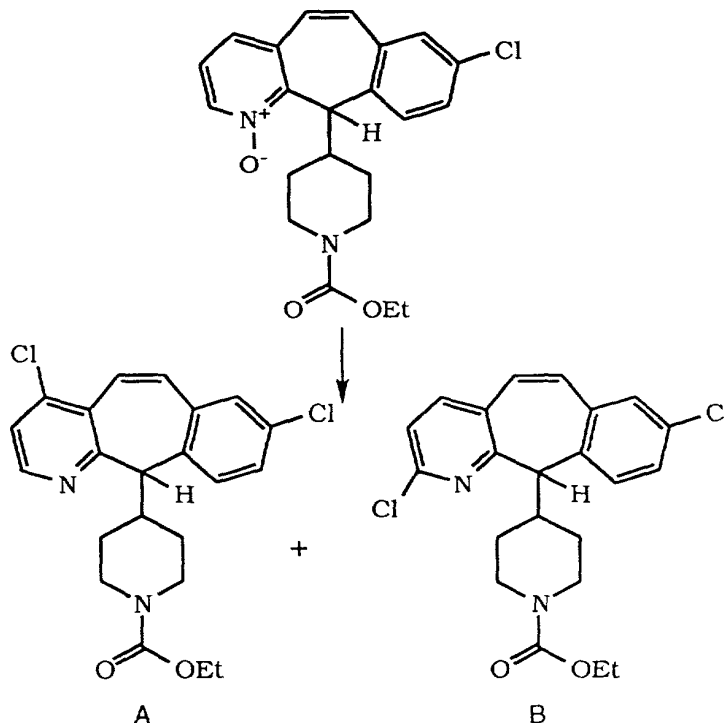
PREPARATIVE EXAMPLE 36

A. 8-CHLORO-11-(1-ETHOXYCARBONYL-4-PIPERIDINYL)-  
11H-BENZO[5.6]CYCLOHEPTA[1.2-b]PYRIDINE-1-OXIDE



- 5           The title compound from Preparative Example 34A above (20.23 grams, 52.84 mmoles) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (250 mL). MCPBA (1.25 equivalents) was added in one portion and this solution was stirred for 45 minutes. Sodium bisulfite solution (20% w/v) was added and the biphasic mixture rapidly stirred for 30 minutes. The layers were separated and the
- 10   organic layer was washed with saturated Na<sub>2</sub>CO<sub>3</sub> solution and dried with Na<sub>2</sub>SO<sub>4</sub>. Filtration and evaporation afforded the title compound (21g, 99%, mp 78.6-89.4°C, MH<sup>+</sup> 399).

B. 4,8-DICHLORO-11-(1-ETHOXYCARBONYL-4-PIPERIDINYL)-11H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDINE (A) and  
2,8-DICHLORO-11-(1-ETHOXYCARBONYL-4-PIPERIDINYL)-11H-BENZO[5,6]CYCLOHEPTA[1,2-B]PYRIDINE (B)



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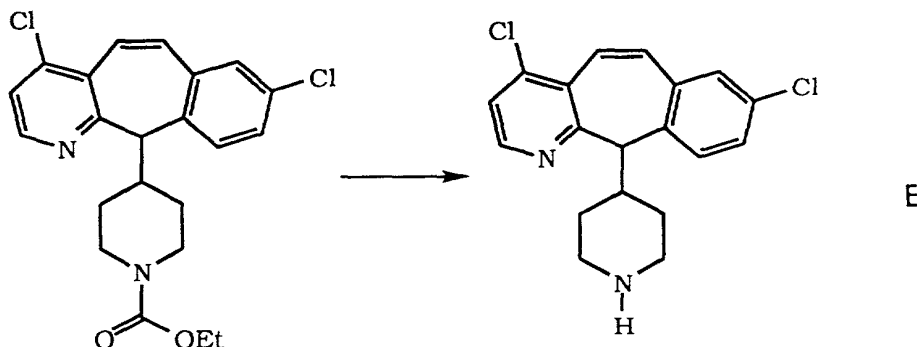
The title compound from Preparative Example 36A (21 grams, 53 mmoles) above was dissolved in anhydrous dichloroethane (250 mL) and the solution cooled to 0°C. POCl<sub>3</sub> (49.4 grams, 0.322 mole) was added dropwise to the dichloroethane solution over 15 minutes. After the POCl<sub>3</sub> was added the reaction mixture was warmed to 45 - 50°C and stirred for 18h. Additional POCl<sub>3</sub> (8.2 grams) was added and the mixture heated to reflux for 9h. The mixture was cooled and added to an ice cooled, stirred solution of NaOH (15% w/v). The resulting biphasic mixture was stirred rapidly for 18h. The layers were separated and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were washed with water followed by brine and dried (Na<sub>2</sub>SO<sub>4</sub>). The mixture was filtered and evaporated, and the residue chromatographed on silica gel using a gradient of 25% EtOAc in hexane to 45% EtOAc in hexane as eluent. The title compound A was obtained as a yellow solid (5.98 g M<sup>+</sup> 417), and title compound B was obtained as a yellow solid (1.0 g, mp 84.4-90.6°C).

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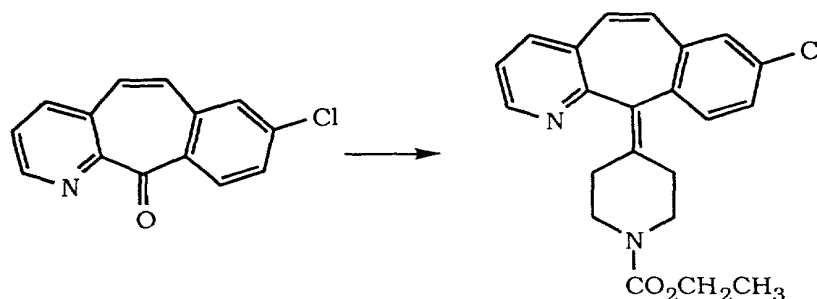
C. 4,8-DICHLORO-11-(4-PIPERIDINYL)-11H-BENZO[5,6]-CYCLOHEPTA[1,2-b]PYRIDINE



- 5 The title compound A from Preparative Example 36B was hydrolyzed under the conditions described in Preparative Example 34C to give the title compound ( $M^+$  345).

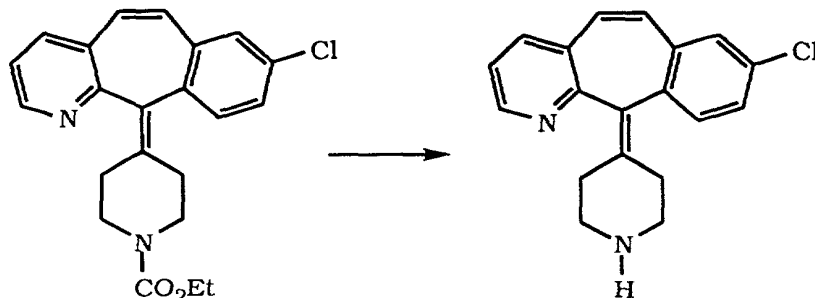
PREPARATIVE EXAMPLE 37

10 A. 4-(8-CHLORO-11H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11-YLIDENE)-1-(ETHOXYCARBONYL)-PIPERIDINE



- 15 The preparation of the starting material for this reaction was described in *The Journal of Organic Chemistry*, **1990**, 55, pp. 3341-3350 by Piwinski, *et al.* By substituting in Preparative Example 2, 8-chloro-11H-benzo[5,6]-cyclohepta[1,2-b]pyridin-11-one for 9-fluoro-5,6-dihydro-11H-benzo[5,6]-cyclohepta[1,2-b]pyridin-11-one and employing basically the same methods as steps D through F of Preparative Example 2, one obtains the title compound (mp 154.7 - 155.5°C).

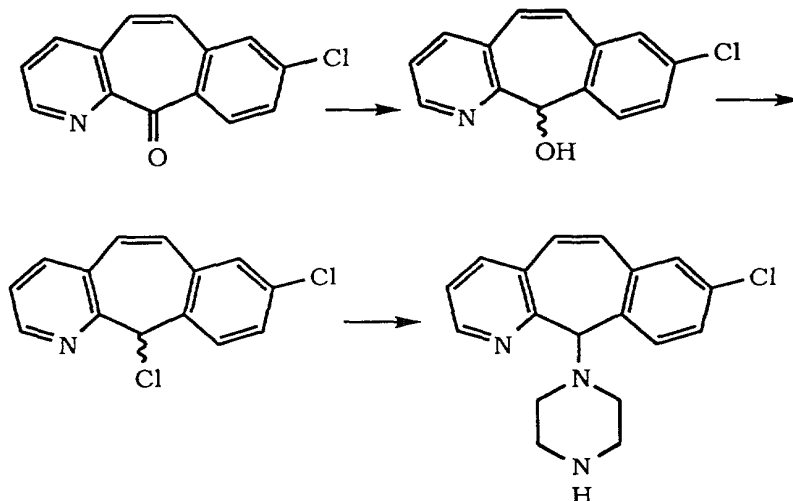
B. 8-CHLORO-11-(4-PIPERIDINYL)-BENZO[5,6]CYCLO-  
HEPTA[1,2-b]PYRIDINE



Hydrolyze the title compound of Preparative Example 37A following  
5 the procedure described in Preparative Example 334C (mp 168.5 -  
171.2°C, decomposition).

PREPARATIVE EXAMPLE 38

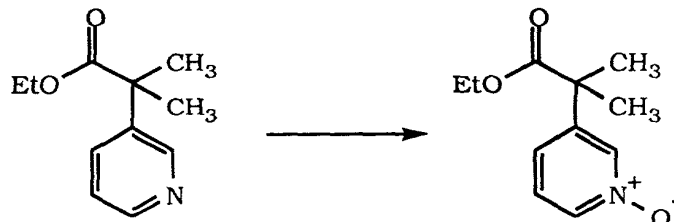
10 8-CHLORO-11-(1-PIPERAZINYL)-11H-BENZO[5,6]CYCLO-  
HEPTA[1,2b]PYRIDINE



The preparation of the starting material for this reaction was  
described in *The Journal of Organic Chemistry*, **1990**, *55* , pp. 3341-3350  
by Piwinski, J.J., *et al.* By substituting in Preparative Example 7A, 8-  
15 chloro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-one (11.53g)  
(47.71mmoles) for 8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-  
b]pyridin-11-one and employing basically the same methods as steps A  
through C of Preparative Example 7, one obtains 11.53g (36%) of the title  
20 compound (MH<sup>+</sup> 312).

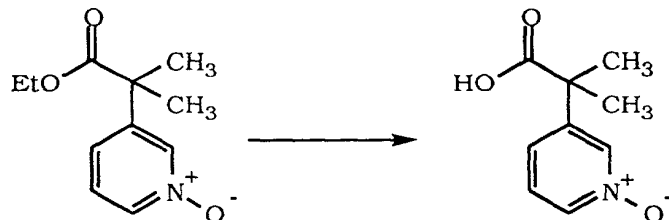
PREPARATIVE EXAMPLE 39

A. ETHYL  $\alpha,\alpha$ -DIMETHYL-3-PYRIDYLACETIC ACID N-OXIDE



By substituting in Preparative Example 8A, ethyl  $\alpha,\alpha$ -dimethyl-3-pyridylacetic acid (4.0g, 20.7mmoles) for ethyl 3-pyridylacetic acid and using the same method as described in Preparative Example 8A, one obtains the title compound (3.2g, 74%,  $MH^+$  210).

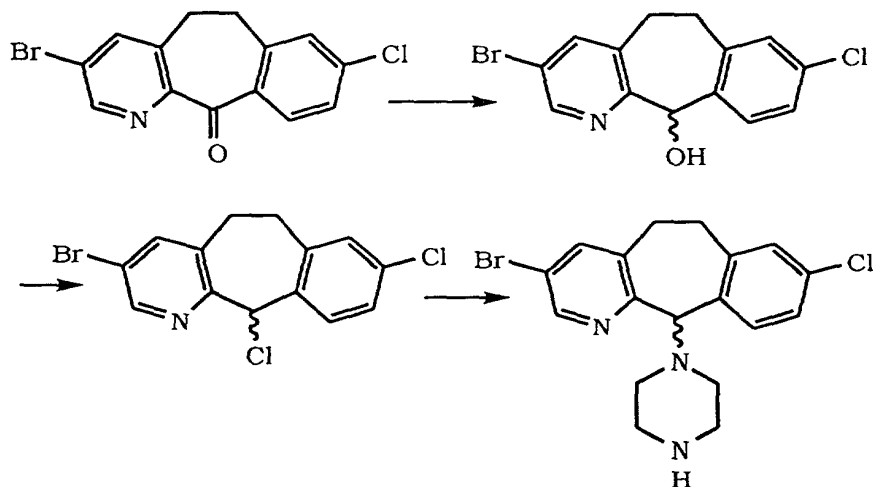
B.  $\alpha,\alpha$ -DIMETHYL-3-PYRIDYLACETIC ACID N-OXIDE



By substituting in Preparative Example 8B, ethyl  $\alpha,\alpha$ -dimethyl-3-pyridylacetic acid N-oxide (0.142g, 0.68mmoles) (Preparative Example 39A) for ethyl 3-pyridylacetic acid N-oxide and using the same method as described in Preparative Example 8B, one obtains the title compound.

PREPARATIVE EXAMPLE 40

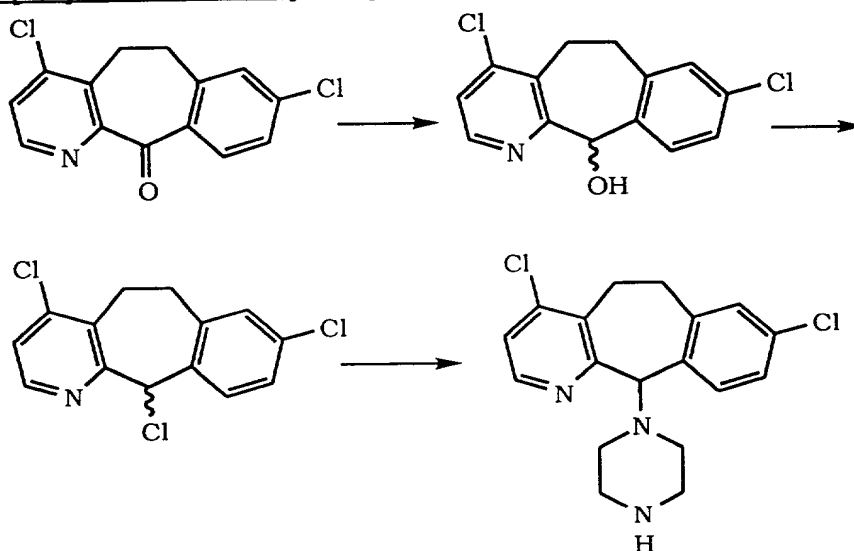
4-BROMO-8-CHLORO-11-(1-PIPERAZINYL)-6,11-DIHYDRO-5H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDINE



By substituting in Preparative Example 7A, 4-bromo-8-chloro-11-(1-piperazinyl)-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-one (1.5g, 4.65mmoles) (Preparative Example 20A) for 8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-one and using the same methods as described in steps A through C of Preparative Example 7, one obtains the title compound (1.31g, 72%,  $MH^+$  392).

PREPARATIVE EXAMPLE 41

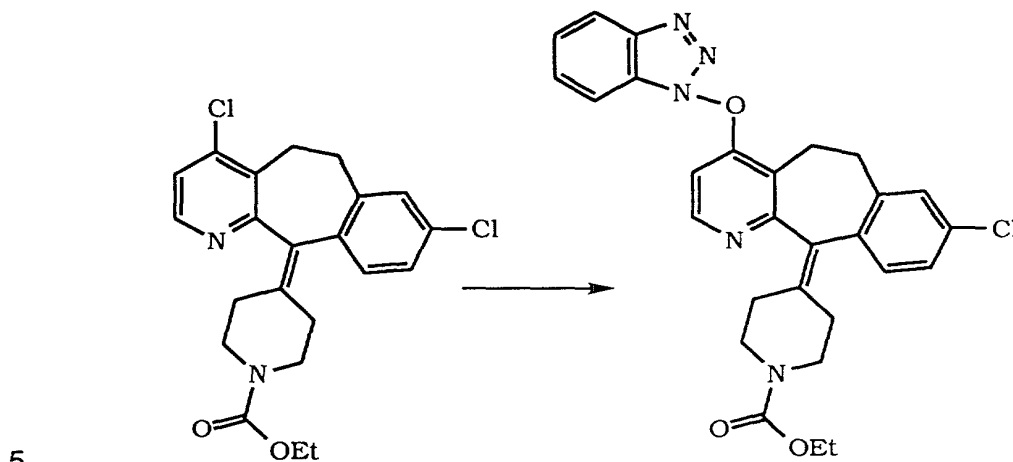
4,8-DICHLORO-11-(1-PIPERAZINYL)-6,11-DIHYDRO-5H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDINE



By substituting in Preparative Example 7A 4,8-Dichloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-one (6.64g, 28.37mmoles) (Preparative Example 5B) for 8-chloro-5,6-dihydro-11H-benzo[5,6] cyclohepta [1,2-b]pyridin-11-one and using the same methods as described in steps A through C of Preparative Example 7, one obtains the title compound (2.59g, 26%,  $MH^+$  348).

PREPARATIVE EXAMPLE 42

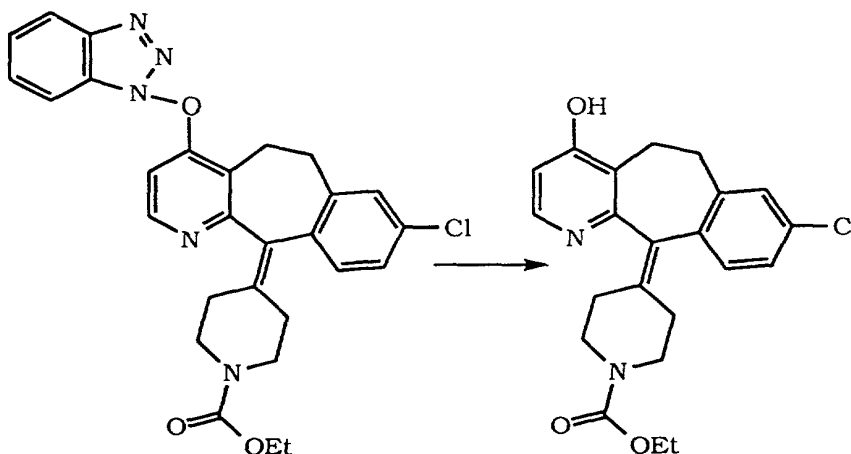
ETHYL 4-[4-[(1H-BENZOTRIAZOL-1-YL)OXY]-8-CHLORO-5,6-DIHYDRO-11H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11-YLIDENE]-1-PIPERIDINE CARBOXYLATE



To a solution of the 4,8-dichloro compound from Preparative Example 27 (1.5 grams) in dry DMF (20 mL) was added HOBT (1.5 grams). After stirring for 14 days at 25°C, NaH (0.84 grams, 60% in mineral oil) was added and after an additional 24 hours, the mixture was poured into water. Filtration provided the title compound (Yield: 1.7 grams, 89%, mp = 181.5 - 183.9 °C, MH<sup>+</sup> 516).

PREPARATIVE EXAMPLE 43

15 ETHYL 4-[4-HYDROXY-8-CHLORO-5,6-DIHYDRO-11H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11-YLIDENE]-1-PIPERIDINE CARBOXYLATE

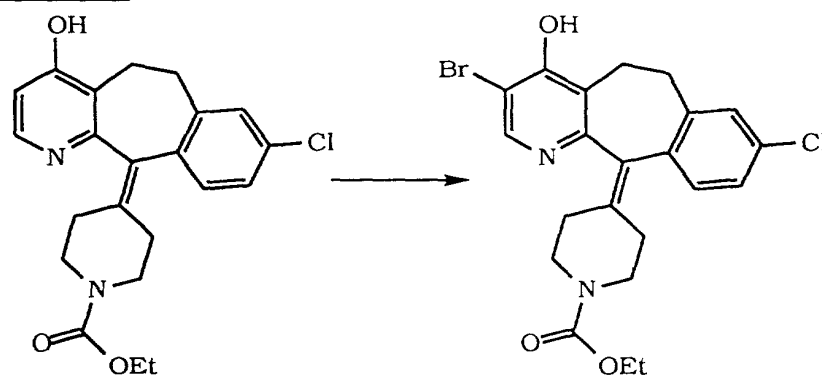


To a solution of the title compound from Preparative Example 42 (0.15 grams) and glacial HOAc (5 mL) was added Zn dust (0.2 grams).

After stirring at 25°C for 1 hour, the mixture was filtered through celite and the filtrate concentrated *in vacuo*. The residue was diluted with EtOAc, washed with saturated aqueous NaHCO<sub>3</sub> and brine. The organic layer was separated, dried over MgSO<sub>4</sub> and concentrated *in vacuo* to give the title compound (Yield: 0.11 grams, 95%, MH<sup>+</sup> 399).

PREPARATIVE EXAMPLE 44

ETHYL 4-[3-BROMO-4-HYDROXY-8-CHLORO-5,6-DIHYDRO-11H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11-YLIDENE]-1-PIPERIDINE  
CARBOXYLATE

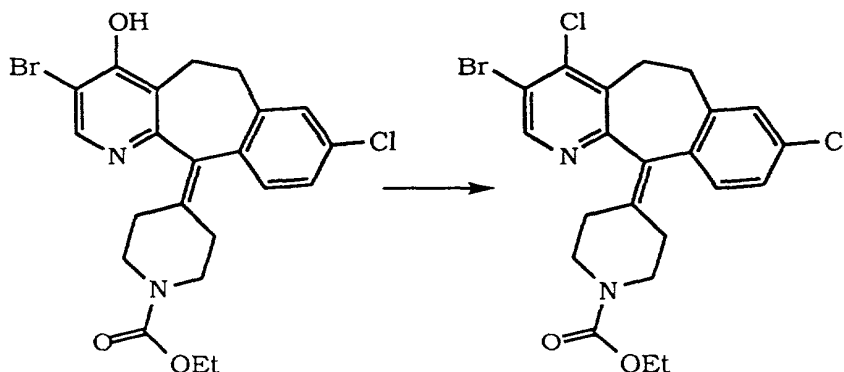


To a solution of the title compound from Preparative Example 43 (1.3 grams) and glacial HOAc (5 mL) was added a 0.7 M bromine-HOAc solution (4 mL) at 25°C under N<sub>2</sub>. The solution was poured into 200 mL of water and the resulting solid was filtered, then washed with water. The solid was dried under vacuum overnight to provide the title compound (Yield: 1.2 grams, 81%, MH<sup>+</sup> 477).



PREPARATIVE EXAMPLE 45

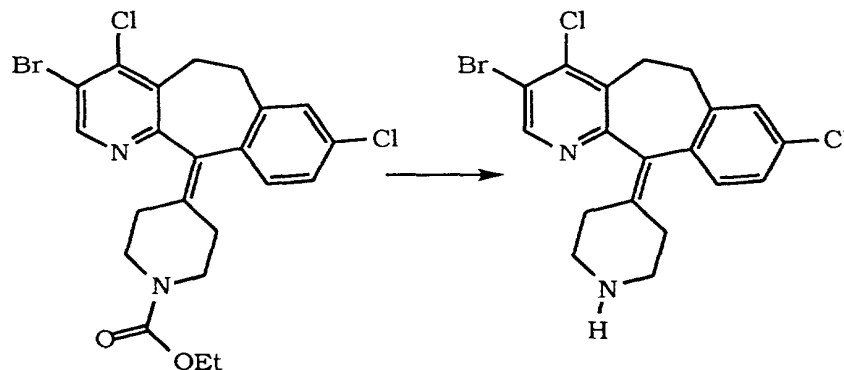
ETHYL 4-[3-BROMO-4,8-DICHLORO-5,6-DIHYDRO-11H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11-YLIDENE]-1-PIPERIDINE CARBOXYLATE



5 A mixture of the title compound from Preparative Example 44 (5.1 grams), phosphorous oxychloride (20 mL) and  $\text{CHCl}_3$  (40 mL) was stirred at reflux over night. The reaction mixture was made basic by the slow addition of 1N aqueous NaOH, and the resultant mixture was diluted with  
10  $\text{CH}_2\text{Cl}_2$ . The mixture was shaken well and after separation of the phases, the organic phase was washed with 1 N aqueous NaOH. The organic phase was dried over anhydrous  $\text{MgSO}_4$ , filtered and concentrated *in vacuo* to provide a solid which was mixed with MeOH and filtered. Concentration of the filtrate provided the title compound as a solid (Yield:  
15 5.7 grams,  $\text{MH}^+$  497).

PREPARATIVE EXAMPLE 46

3-BROMO-4,8-DICHLORO-11-(4-PIPERIDYLIDENE)-6,11-5H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDINE



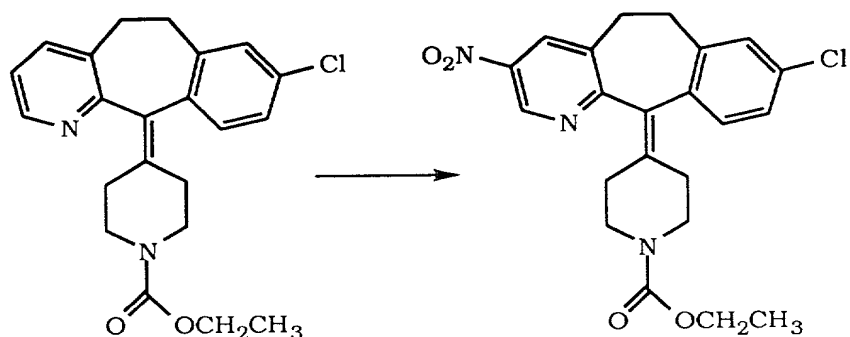
20 A solution of the title compound from Preparative Example 45 (5.7 grams) dissolved in absolute EtOH (100 mL) and concentrated HCl (200 mL) was stirred at reflux for 24 hours. The reaction mixture was cooled in

an ice-water bath and was made basic by the addition of solid KOH. Extraction with CH<sub>2</sub>Cl<sub>2</sub> and concentration of the organic phase *in vacuo* afforded the title compound as a solid (1.7 grams, 35% yield, MH<sup>+</sup> 425).

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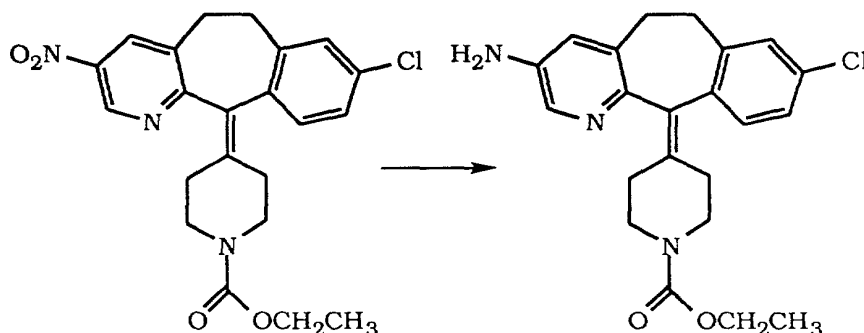
PREPARATIVE EXAMPLE 47

A. 4-(8-CHLORO-3-NITRO-5,6-DIHYDRO-11H-BENZO[5,6]-CYCLOHEPTA[1,2-b]PYRIDIN-11-YLIDENE)-1-PIPERIDINE-1-CARBOXYLIC ACID ETHYL ESTER



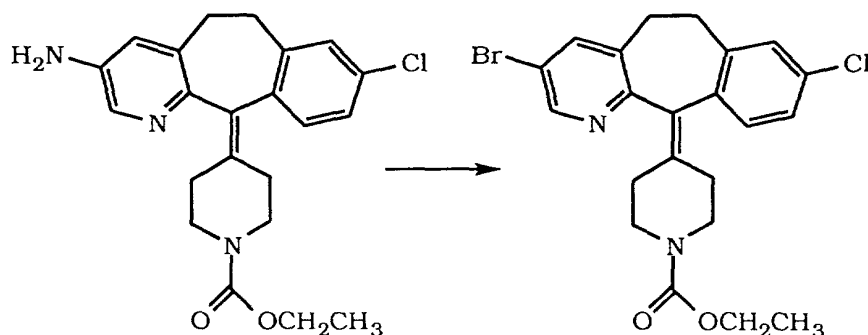
- 10 Tetrabutyl ammonium nitrate(4.98g, 16.3 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub>(20 mL) and TFAA(3.12g,14.9 mmol, 2.1 mL) was then added. The solution was cooled to 0°C and then added (by cannulation) to a solution of 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]-cyclohepta[1,2-b]pyridin-11-ylidene)-1-piperidine-1-carboxylic acid ethyl ester (5.69g, 14.9 mmol) in
- 15 CH<sub>2</sub>Cl<sub>2</sub> (35 mL) also cooled to 0°C. The reaction mixture was stirred at 0°C for 3h and then allowed to go to room temperature (25°C) overnight. The reaction mixture was then extracted with saturated NaHCO<sub>3</sub> (60 mL) dried over MgSO<sub>4</sub> and concentrated to give a semi-solid material that was chromatographed on silica gel eluting first with 10% and then 20% EtOAc
- 20 -hexane. Removal of the organic solvents gave the title compound in 44% yield as a light yellow solid. MP = 90.4-91.0°C, MH<sup>+</sup> 428.

B. 4-(8-CHLORO-3-AMINO-5,6-DIHYDRO-11H-BENZO[5,6]-CYCLOHEPTA[1,2-b]PYRIDIN-11-YLIDENE)-1-PIPERIDINE-1-CARBOXYLIC ACID ETHYL ESTER



5 The title compound from Preparative Example 47A (5.99g, 14 mmol) was dissolved in 85% aqueous EtOH. To this solution was added iron filings (7.01g, 125.57 mmol) and CaCl<sub>2</sub> (0.69g, 6.29 mmol) and the reaction mixture was refluxed for 16h. The reaction mixture was filtered through a bed of celite while hot and the celite was washed with hot EtOH  
10 (700 mL). The EtOH solution was then decolorized with activated charcoal (2.4g) and then filtered through celite. EtOH was then rotary eavaporated to give the title compound in 100% yield as an off-white solid. MP= 102.4-103.1°C, MH + 398.

15 C. 4-(8-CHLORO-3-BROMO-5,6-DIHYDRO-11H-BENZO[5,6]-CYCLOHEPTA[1,2-b]PYRIDIN-11-YLIDENE)-1-PIPERIDINE-1-CARBOXYLIC ACID ETHYL ESTER



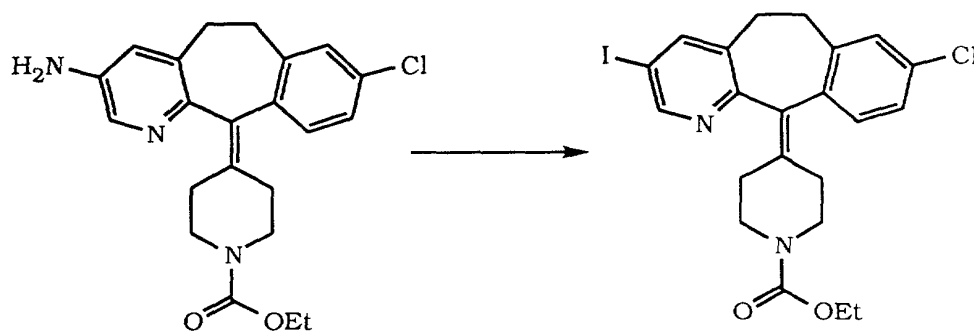
20 The title compound from Preparative Example 47B (3.00g, 7.60 mmol) was dissolved in HBr (48%, 30 mL). The reaction mixture was cooled to -5°C (ice-ethylene glycol bath) and bromine(2 mL) was added dropwise. The reaction mixture was stirred at -5°C for 15 minutes. Sodium nitrite (1.57g, 22.8 mmol) dissolved in water (15 mL) was slowly added to the reaction mixture. The reaction mixture was then stirred for 45 minutes and then quenched with 40% NaOH to pH ~10. The aqueous

phase was then extracted with EtOAc(3x100mL). Combined EtOAc fractions were dried over Na<sub>2</sub>SO<sub>4</sub> and then concentrated to give the title compound in 83% yield as a light brown solid. Mp = 146-148°C, MH<sup>+</sup> 463.

5

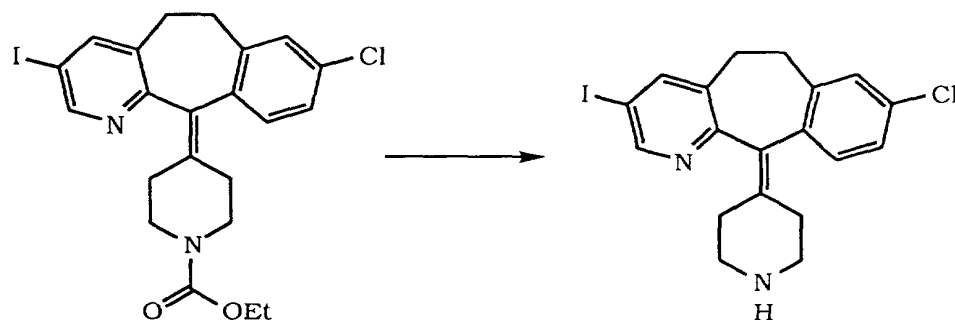
#### PREPARATIVE EXAMPLE 48

##### Step A:



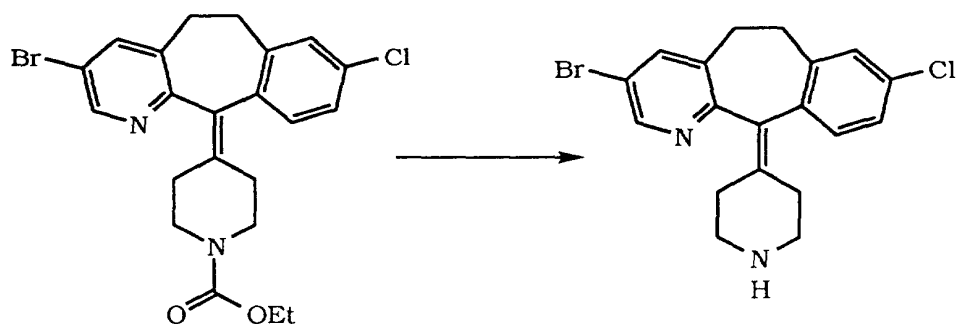
Combine 6 g (15.11 mmol) of the title compound of Preparative  
10 Example 47B and benzene, and add 2.3 g (9.06 mmol) of iodine. Heat the  
mixture at reflux for 3 hours, cool, then dilute with 50 mL of CH<sub>2</sub>Cl<sub>2</sub>. Wash  
the organic phase with 5% NaHSO<sub>3</sub>(aqueous) (3 x 80 mL), then with 1M  
NaOH (aqueous) (2x 80 mL), and dry over MgSO<sub>4</sub>. Concentrate to a  
15 residue chromatograph (silica gel, 30% EtOAc/hexanes), to give 3.2 g  
(42% yield) of the product iodo compound. Mass Spec., MH<sup>+</sup> = 509

##### Step B:



The product of Step A is hydrolyzed via substantially the same  
20 procedure as described in Example 358, Step A, to give the iodoamine  
product in 89% yield.

PREPARATIVE EXAMPLE 49



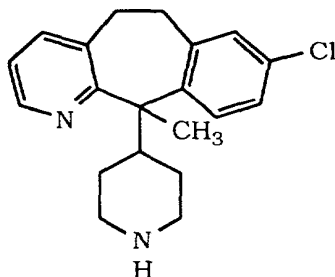
The product of Preparative Example 47, Step C, (2.42 g) is hydrolyzed via substantially the same procedure as described in Example 5 358, Step A, to give 1.39 g (69% yield) of the bromoamine product.

Using the starting compound indicated and following essentially the same procedure as for Preparative Example 49, the following compounds were prepared:

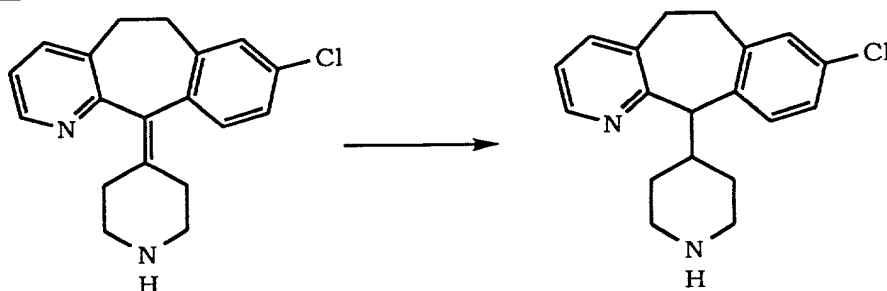
| Starting Compound              | Compound                       | Analytical Data                      |
|--------------------------------|--------------------------------|--------------------------------------|
| Preparative Example 51, Step C | <p>Preparative Example 49A</p> | Mass Spec.:<br>MH <sup>+</sup> = 407 |

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PREPARATIVE EXAMPLE 50

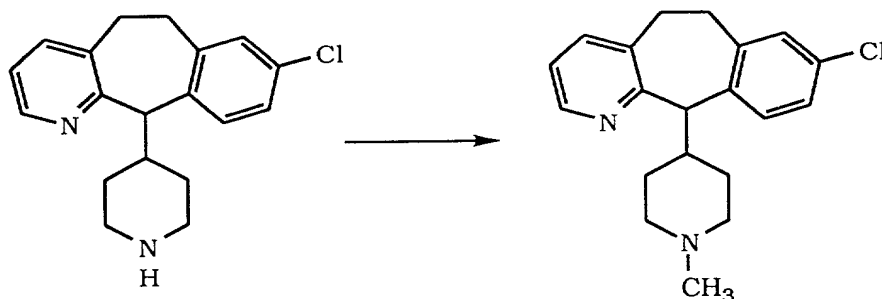


Step A:



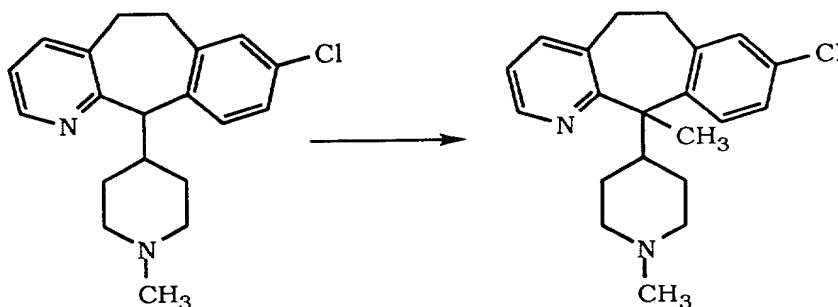
Combine 82.0 g (0.26 mole) of the product of Preparative Example 1, Step G, and 1 L of toluene, then add 20.06 g (0.53 mole) of  $\text{LiAlH}_4$  and heat the reaction mixture at reflux overnight. Cool the mixture to room temperature and add ~1 L of  $\text{Et}_2\text{O}$ , followed by dropwise addition of saturated  $\text{Na}_2\text{SO}_4$  (aqueous) until a precipitate forms. Filter and stir the filtrate over  $\text{MgSO}_4$  for 30 minutes, then concentrate *in vacuo* to give the product compound in 83% yield. Mass Spec.:  $\text{MH}^+ = 313$

Step B:



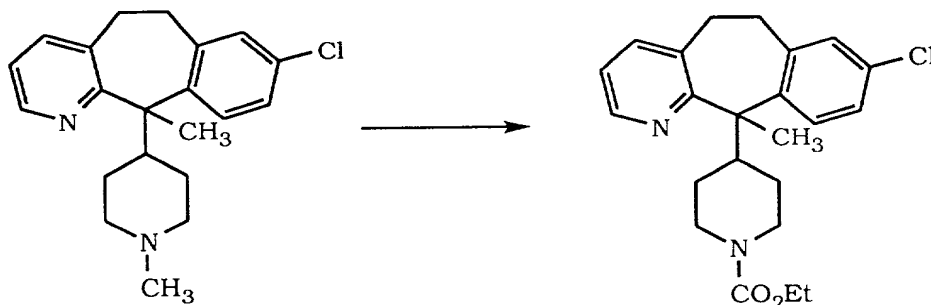
Combine 74 g (0.24 mol) of the Product from Step A and 95 g (6.84 equiv.) of  $\text{HCO}_2\text{H}$ , then add 129 g of 7% formadehyde and heat the mixture to ~80°C for 2 hours. Cool the mixture to room temperature and basify with 25%  $\text{NaOH}$  (aqueous). Extract with  $\text{EtOAc}$  (3 X 1.3 L), dry the extracts over  $\text{Na}_2\text{SO}_4$  and concentrate to a residue. Recrystallize the residue from  $i\text{Pr}_2\text{O}$  and  $\text{Et}_2\text{O}$  to give the product compound. Mass Spec.:  $\text{MH}^+ = 326$ .

Step C:



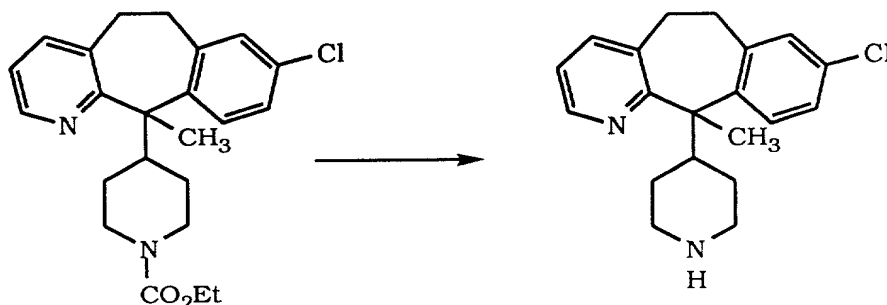
- Combine 28 g of the Product of Step B and 800 mL of THF and cool to -65°C. Add a solution of 41.2 mL (1.2 equiv.) of 2.5 M n-BuLi in  
5 hexanes, stir for 1 hour at -65°C, then warm to -30 °C and stirred at that temperature for 1 hour. Cool to -65°C and add 10.5 mL of CH<sub>3</sub>I, then warm to -10°C and quench with 1.5 mL of Et<sub>2</sub>O followed by 10 mL of NH<sub>4</sub>OH (aqueous). Dry the organic phase over K<sub>2</sub>CO<sub>3</sub> and concentrate *in vacuo* to a residue. Dissolve the residue in CH<sub>2</sub>Cl<sub>2</sub>, wash with H<sub>2</sub>O,  
10 dry over Na<sub>2</sub>SO<sub>4</sub> and concentrate *in vacuo* to give a residue. Chromatograph (silica gel, 5% MeOH/EtOAc + NH<sub>4</sub>OH) to give 26 g of the product compound.

Step D:



- 15 Combine 26 g of the Product of Step C, toluene, and 33 mL (3 equiv.) of Et<sub>3</sub>N, then heat to 70°C. Slowly add 45 mL (6 equiv.) of ClCO<sub>2</sub>Et over a period of 45 min. Stir for 15 min. then pour the mixture into ice and add 100 mL of 1 N NaOH (aqueous). Extract with EtOAc, dry  
20 the extract and concentrate *in vacuo* to give 37 g of the product compound.

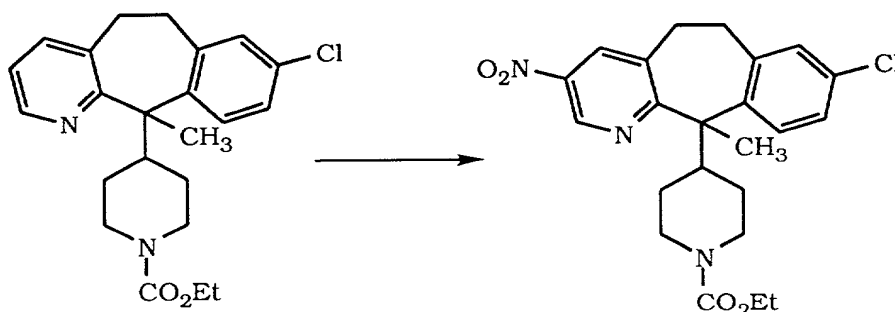
Step E:



Hydrolyze 3.5 g (8.8 mmol) of the Product of Step D, by substantially the same procedure as described for Example 358, Step A, to give 2.26 g (79% yield) of the product compound.  
Mass Spec.:  $MH^+ = 327$

PREPARATIVE EXAMPLE 51

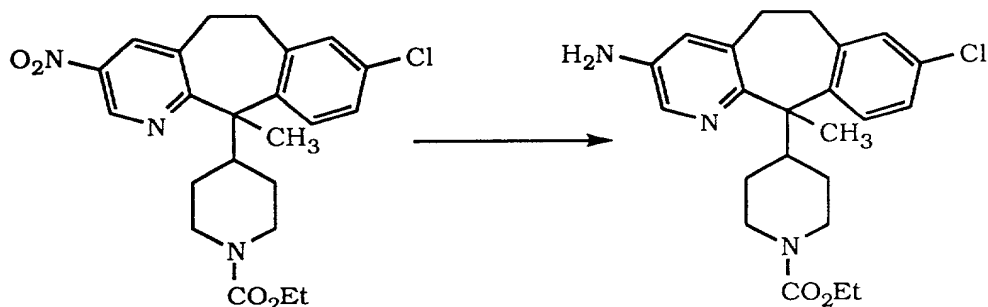
Step A:



Dissolve 8.66 g (28.6 mmol) of tetra-n-butylammonium nitrate in 50 mL of CH<sub>2</sub>Cl<sub>2</sub> and add 5.99 g (28.57 mmol, 2.1 mL) of TFAA. Cool to 0°C and add the mixture (via cannula) to a solution of 10.36 g (14.9 mmol) of the product of Preparative Example 50, Step D in 150 mL of CH<sub>2</sub>Cl<sub>2</sub> at 0°C, then stir at 0°C for 3 hours. Allow the mixture to warm to 25°C while stirring overnight, then extract with 150 mL of saturated NaHCO<sub>3</sub> (aqueous) and dry over MgSO<sub>4</sub>. Concentrate *in vacuo* to a residue and chromatograph the residue (silica gel, 10% EtOAc/hexane, then 20% EtOAc/hexane) to give a 57% yield of the product compound.  
Mass Spec.:  $MH^+ = 442$ .

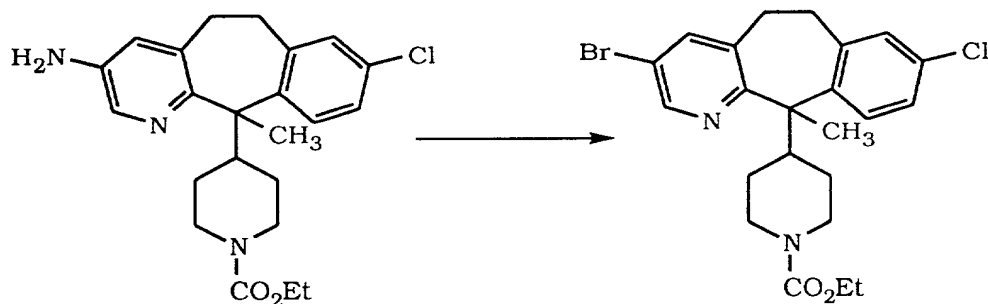


Step B:



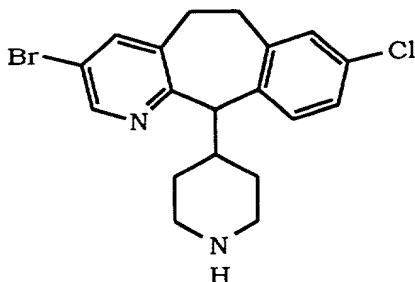
Combine 5.9 g (13.29 mmol) of the Product of Step A and 400 mL of 85% EtOH (aqueous), add 6.6 g (119 mmol) of Fe filings and 0.66 g (5.98 mmol) of  $\text{CaCl}_2$ , and heat at reflux for 16 hours. Filter the hot mixture through a bed of celite®, wash the celite® with 700 mL of hot EtOH. Concentrate the filtrate *in vacuo* to give a 100% yield of the product compound. Mass Spec.:  $\text{MH}^+ = 414$ .

10 Step C:

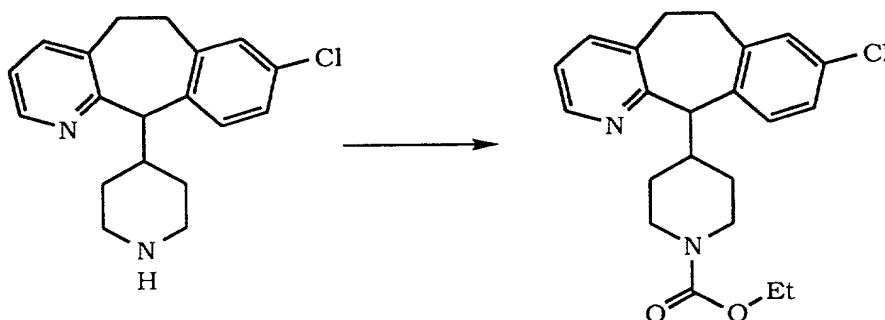


Combine 6.5 g (15.7 mmol) of the Product of Step B and 63 mL of 48% HBr, cool the mixture to  $-5^\circ\text{C}$  and slowly (dropwise) add 4.4 mL of  $\text{Br}_2$  bromine(4.4 mL). Stir the mixture at  $-5^\circ\text{C}$  for 15 minutes and slowly add a solution of 3.25 g (47.1 mmol) of  $\text{NaNO}_2$  in 30 mL of water. Stir for 45 minutes, then quench with 50% NaOH (aqueous) to pH ~10. Extract with EtOAc (3 x 200 mL), dry the combined extracts over  $\text{Na}_2\text{SO}_4$  and concentrate *in vacuo* to give 6.32 g (81% yield) of the product compound. Mass Spec.:  $\text{MH}^+ = 479$

PREPARATIVE EXAMPLE 51A

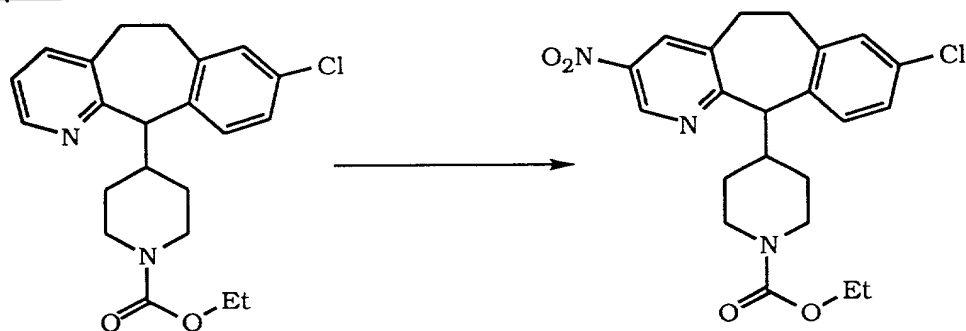


Step A:



- 5            Combine 24.32 g (74.9 mmol) of the Product from Preparative Example 50, Step A, 500 mL of toluene, 83 mL of Et<sub>3</sub>N and 65.9 mL of ethyl chloroformate and heat the mixture at reflux overnight. Cool to 25°C, pour into 200 mL of water and extract with EtOAc. Dry the extract over MgSO<sub>4</sub>, concentrate *in vacuo* to a residue and chromatograph (silica gel, 50% EtOAc/hexane) to give 15 g of the product compound. Mass Spec.: MH<sup>+</sup> = 385.

Step B:



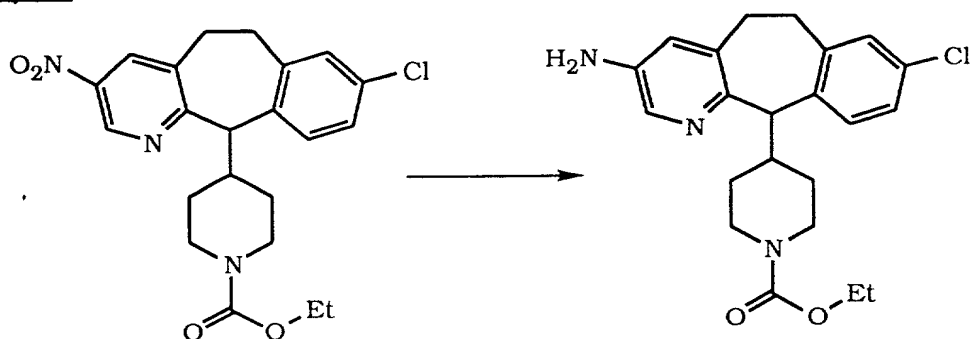
- 15            Dissolve 3.2 g (10.51 mmol) of tetra-n-butylammonium nitrate in 25 mL of CH<sub>2</sub>Cl<sub>2</sub> and add 2.2 g (10.51 mmol, 1.5 mL) of TFAA. Cool to 0°C and add the mixture (via cannula) to a solution of 3.68 g (9.56 mmol) of the product of Step A in 50 mL of CH<sub>2</sub>Cl<sub>2</sub> at 0°C, then stir at 0°C for 3 hours. Allow the mixture to warm to 25°C while stirring overnight, then extract

with saturated  $\text{NaHCO}_3$  (aqueous) and dry over  $\text{MgSO}_4$ . Concentrate *in vacuo* to a residue and chromatograph (silica gel, 30% EtOAc/hexane) to give 1.2 g of the product compound.

Mass Spec.:  $\text{MH}^+ = 430$ .

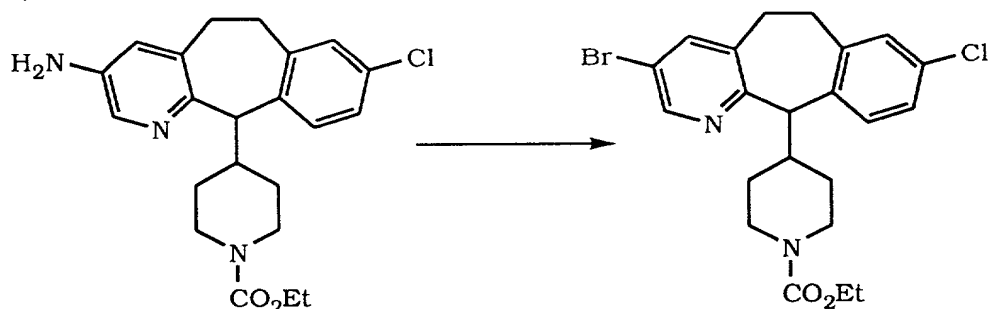
5

Step C:



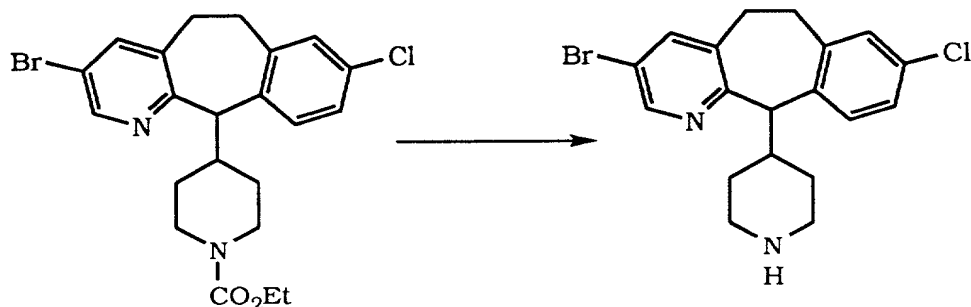
Combine 2.0 g (4.7 mmol) of the Product of Step B and 150 mL of 85% EtOH (aqueous), add 2.4 g (42 mmol) of Fe filings and 0.24 g (2.1 mmol) of  $\text{CaCl}_2$ , and heat at reflux for 16 hours. Filter the hot mixture through a bed of celite®, wash the celite® with hot EtOH. Concentrate the filtrate *in vacuo* to give a 100% yield of the product compound. Mass Spec.:  $\text{MH}^+ = 400$ .

15 Step D:



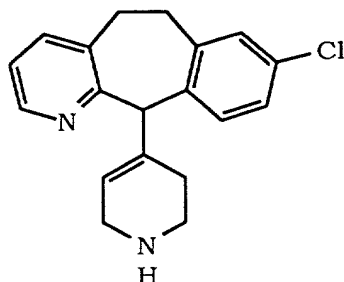
Combine 2.0 g (5.2 mmol) of the Product of Step C and 20 mL of 48% HBr, cool the mixture to  $-5^\circ\text{C}$ . Stir the mixture at  $-5^\circ\text{C}$  for 15 minutes and slowly add a solution of 1.07 g (15.5 mmol) of  $\text{NaNO}_2$  in 10 mL of water. Stir for 45 minutes, then quench with 50% NaOH (aqueous) to pH ~10. Extract with EtOAc, dry the combined extracts over  $\text{MgSO}_4$  and concentrate *in vacuo* to give the product compound. Mass Spec.:  $\text{MH}^+ = 465$

Step E:

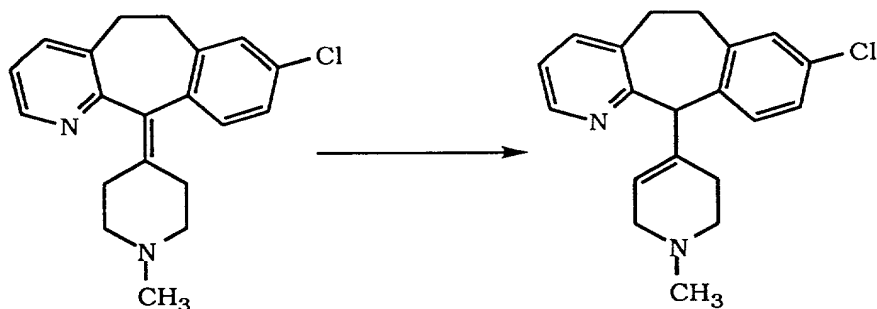


- Hydrolyze 4.0 g of the Product of Step D via substantially the same process as described for Example 358, Step A, to give 1.39 g of the product compound. Mass Spec.:  $MH^+ = 392$
- 5

PREPARATIVE EXAMPLE 52

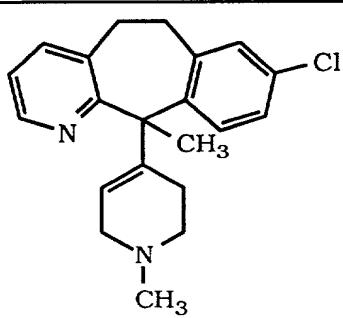


10 Step A:



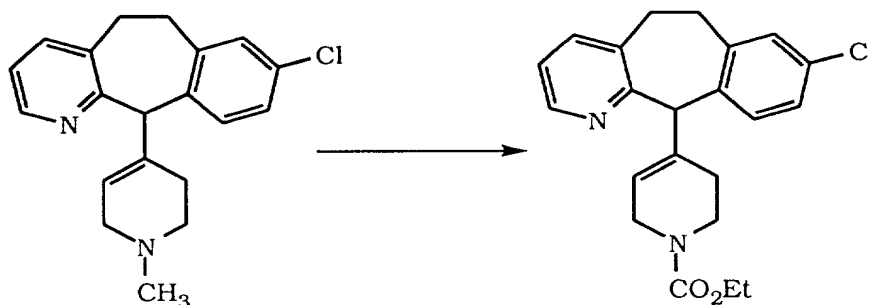
- Dissolve 9.8 g (30.2 mmol) of the Product of Preparative Example 1, Step E, in THF under nitrogen, cool the mixture to  $-15^{\circ}\text{C}$ , then add 17.76 mL (30.3 mmol) of 2.5 M n-butyllithium in hexanes and stir for 1.5 hours. Cool the reaction mixture to  $-70^{\circ}\text{C}$  and add 2.45 mL (60 mmol) of MeOH and warm to room temperature overnight. Add 300 mL of (Et<sub>2</sub>O) and extract with water (3 x 100 mL). Dry the extracts, concentrate *in vacuo* to a residue and chromatograph the residue (silica gel, 5% Et<sub>3</sub>N/EtOAc) to give 6.59 g (68% yield) of the product compound.
- 15

Via substantially the same procedure as described in Preparative Example 52, Step A, except that methyl iodide is used in place of MeOH, the following product compound is prepared:

| Starting Compound             | Compound   | Analytical Data                      |
|-------------------------------|--|--------------------------------------|
| Preparative Example 1, Step E |  <p>Preparative Example 52A</p> | Mass Spec.:<br>MH <sup>+</sup> = 339 |

5

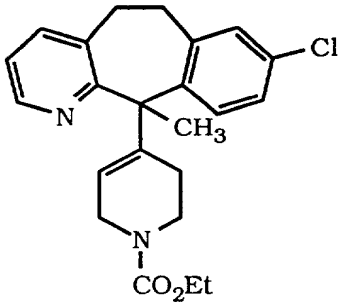
Step B:



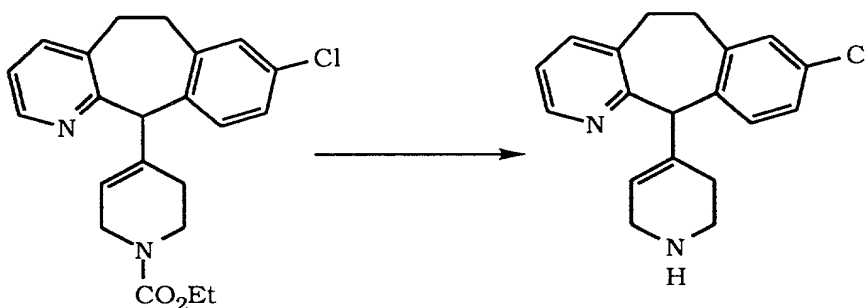
Treat 3 g (9.23 mmol) of the Product of Step A with 10 mL of ClCO<sub>2</sub>Et and 10 mL of Et<sub>3</sub>N via substantially the same procedure as described in Preparative Example 50, Step D, to give 2.2 g (64% yield) of the product compound. Mass Spec.: MH<sup>+</sup> = 383

10

Using the starting compound indicated and substantially the same procedure as described in Preparative Example 52, Step B, the following product compound is prepared:

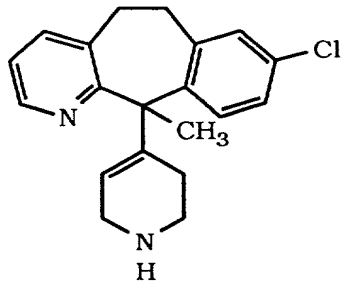
| Starting Compound               | Compound   | Analytical Data                      |
|---------------------------------|--|--------------------------------------|
| Preparative Example 52A, Step A |  <p>Preparative Example 52A</p> | Mass Spec.:<br>MH <sup>+</sup> = 397 |

Step C:

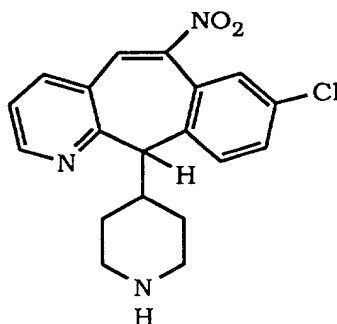


- 5      Treat the Product of Step B via substantially the same procedure as described in Preparative Example 1, Step F, to give the product compound. Mass Spec.: MH<sup>+</sup> = 310

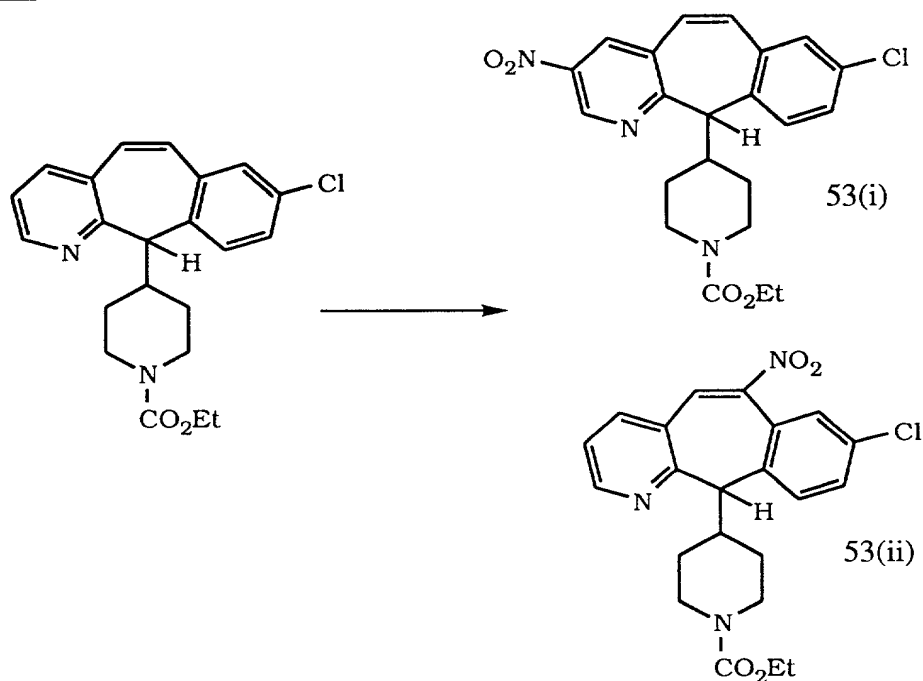
- 10      Using the starting compound indicated and substantially the same procedure as described in Preparative Example 52, Step C, the following product compound is prepared:

| Starting Compound               | Compound   | Analytical Data                      |
|---------------------------------|--|--------------------------------------|
| Preparative Example 52A, Step B |  <p>Preparative Example 52A</p> | Mass Spec.:<br>MH <sup>+</sup> = 325 |

PREPARATIVE EXAMPLE 53



5 Step A:

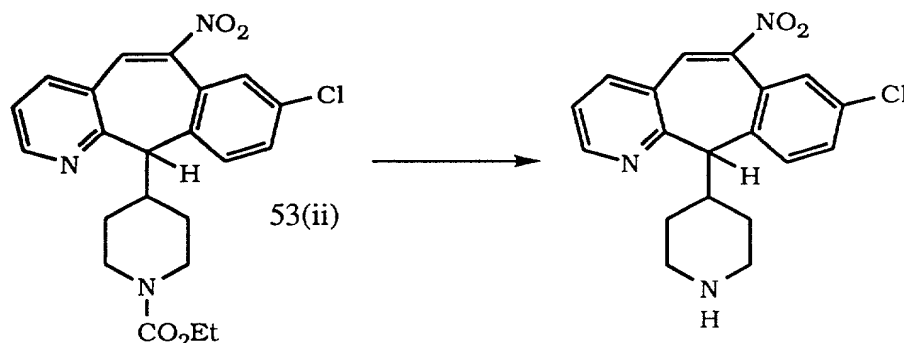


Combine 14.95 g (39 mmol) of the Product of Preparative Example 34A and 150 mL of CH<sub>2</sub>Cl<sub>2</sub>, then add 13.07 g (42.9 mmol) of (nBu)<sub>4</sub>NNO<sub>3</sub> and cool the mixture to 0°C. Slowly add (dropwise) a solution of 6.09 mL (42.9 mmol) of TFAA in 20 mL of CH<sub>2</sub>Cl<sub>2</sub> over 1.5 hours. Keep the mixture at 0°C overnight, then wash successively with saturated NaHCO<sub>3</sub> (aqueous), water and brine. Dry the organic solution over Na<sub>2</sub>SO<sub>4</sub>, concentrate *in vacuo* to a residue and chromatograph the residue (silica gel, EtOAc/hexane gradient) to give 4.32 g and 1.90 g of the two product compounds 53(i) and 53(ii), respectively.

Mass Spec. for compound 53(i): MH<sup>+</sup> = 428.2;

Mass Spec. for compound 53(ii): MH<sup>+</sup> = 428.3

**Step B:**



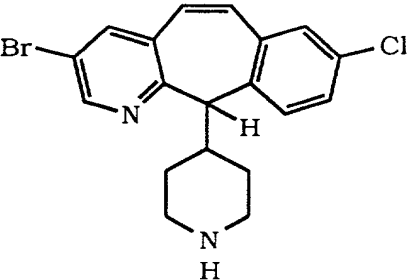
The compound 53(ii) from Step A (0.20 g) is hydrolyzed via substantially the same procedure as described for Example 358, Step A, to give 0.16 g of the product compound.

Using the starting compound indicated and substantially the same procedure as described in Preparative Example 53, Step B, the following product compound is prepared:

10

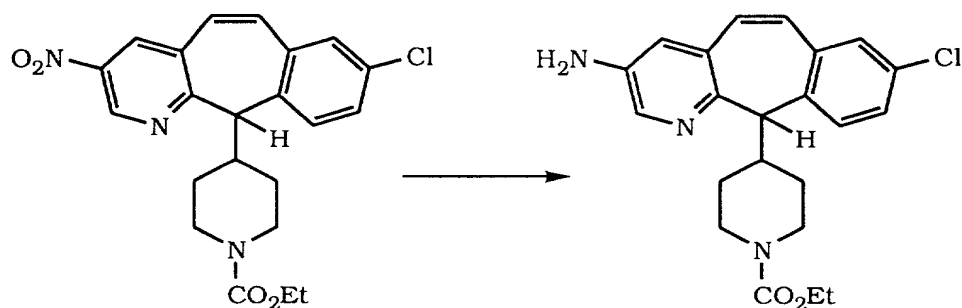
| Starting Compound                               | Compound   | Analytical Data                        |
|---|--|--|
| Preparative Example 53, Step A, compound 53(i)  | <p style="text-align: center;">Preparative Example 53A</p> | ---                                    |
| Preparative Example 54, Step B, compound 54(ii) | <p style="text-align: center;">Preparative Example 53B</p> | Mass Spec.:<br>MH <sup>+</sup> = 466.9 |



|   |   |   |
|---|---|---|
| <p>Preparative<br/>Example 54,<br/>Step B,<br/>compound<br/>54(i)</p> |  <p>Preparative Example 53C</p> | <p>Mass Spec.:<br/>MH<sup>+</sup> = 466.9</p> |
|---|---|---|

### PREPARATIVE EXAMPLE 54

#### Step A:



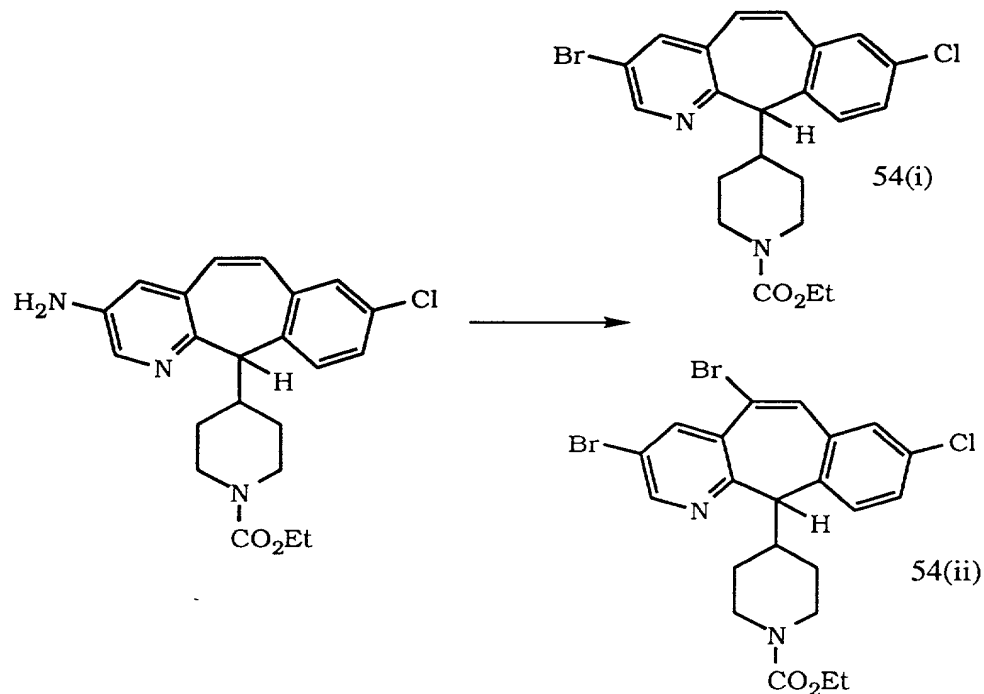
5

Combine 22.0 g (51.4 mmol) of the product 53(i) from Preparation 53, Step A, 150 mL of 85% EtOH (aqueous), 25.85 g (0.463 mole) of Fe powder and 2.42 g (21.8 mmol) of CaCl<sub>2</sub>, and heat at reflux overnight. Add 12.4 g (0.222 mole) of Fe powder and 1.2 g (10.8 mmol) of CaCl<sub>2</sub> and heat at reflux for 2 hours. Add another 12.4 g (0.222 mole) of Fe powder and 1.2 g (10.8 mmol) of CaCl<sub>2</sub> and heat at reflux for 2 hours more. Filter the hot mixture through celite®, wash the celite® with 50 mL of hot EtOH and concentrate the filtrate *in vacuo* to a residue. Add 100 mL of anhydrous EtOH, concentrate to a residue and chromatograph the residue (silica gel, MeOH/CH<sub>2</sub>Cl<sub>2</sub> gradient) to give 16.47 g of the product compound.

10

15

Step B:



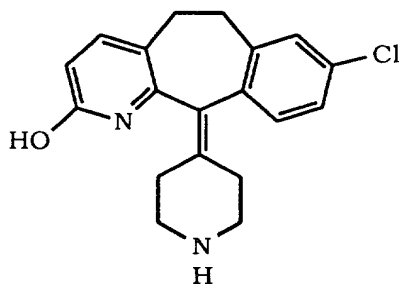
- Combine 16.47 g (41.4 mmol) of the product compound from Preparative Example 54, Step A, and 150 mL of 48% HBr (aqueous) and cool to -3°C. Slowly add (dropwise) 18 mL of bromine, then slowly add (dropwise) a solution of 8.55 g (0.124 mole) of NaNO<sub>3</sub> in 85 mL of water. Stir for 45 minutes at -3° to 0°C, then adjust to pH = 10 by adding 50% NaOH (aqueous). Extract with EtOAc, wash the extracts with brine and dry the extracts over Na<sub>2</sub>SO<sub>4</sub>. Concentrate to a residue and chromatograph (silica gel, EtOAc/hexane gradient) to give 10.6 g and 3.28 g of the two product compounds 54(i) and 54(ii), respectively.

Mass Spec. for compound 54(i): MH<sup>+</sup> = 461.2;

Mass Spec. for compound 54(ii): MH<sup>+</sup> = 539

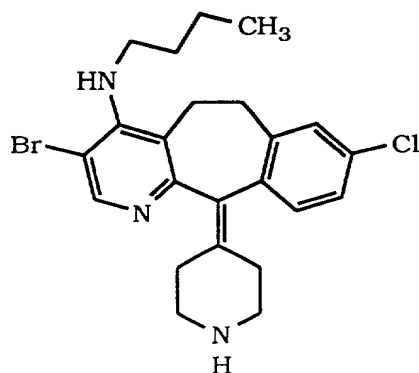
15

PREPARATIVE EXAMPLE 55



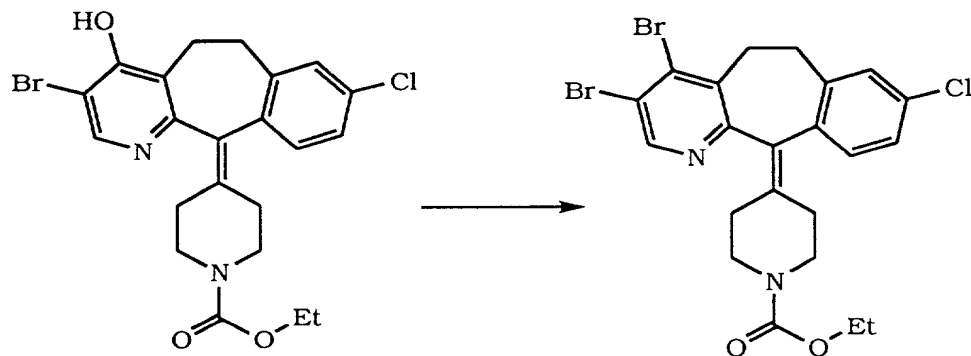
The title compound is known and is prepared by the procedure described in Bioorg. & Med. Chem. Lett., **3**, (No. 6) 1073-1078 (1993).

PREPARATIVE EXAMPLE 56



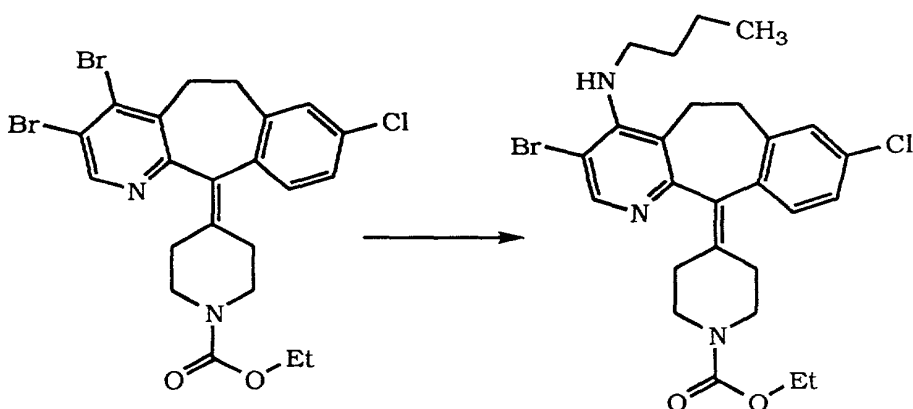
5

Step A:



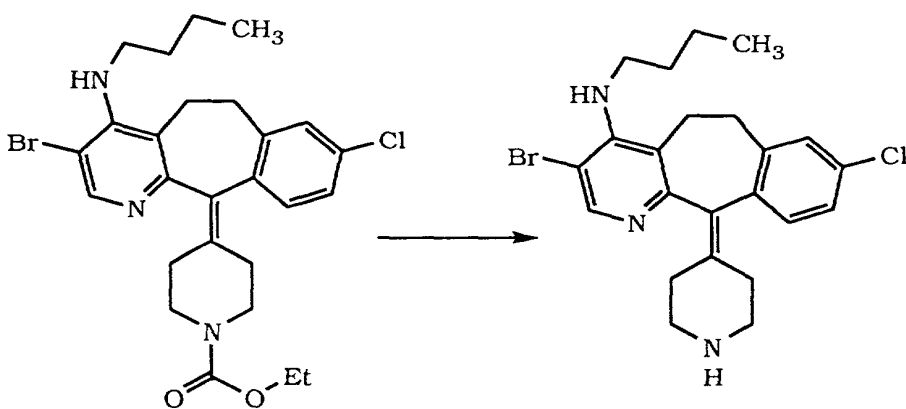
10 Combine 2.04 g of the product of Preparative Example 44, 1.3 mL of  $\text{PBr}_3$ , 1.0 mL of  $\text{Et}_3\text{N}$  and 20 mL of  $\text{CH}_2\text{Br}_2$ , and heat the mixture at reflux overnight. Cool the mixture, dilute with  $\text{CH}_2\text{Cl}_2$  and wash with 1 N  $\text{NaOH}$  (aqueous). Dry over  $\text{MgSO}_4$  and concentrate *in vacuo* to give 1.22 g (53% yield) of the product compound. Mass Spec.:  $\text{MH}^+ = 541$

Step B:



Combine 0.3 g of the product compound from Preparative Example 56, Step A, and 8 mL of n-butylamine and stir at 120°C in a sealed tube for 48 hours. Concentrate *in vacuo* to a residue and purify by preparative plate chromatography (silica gel, 1.5-2.5% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to give 80 mg (27%) yield of the product compound. Mass Spec.: MH<sup>+</sup> = 534

Step C:

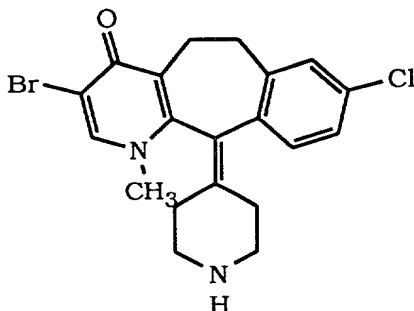


10

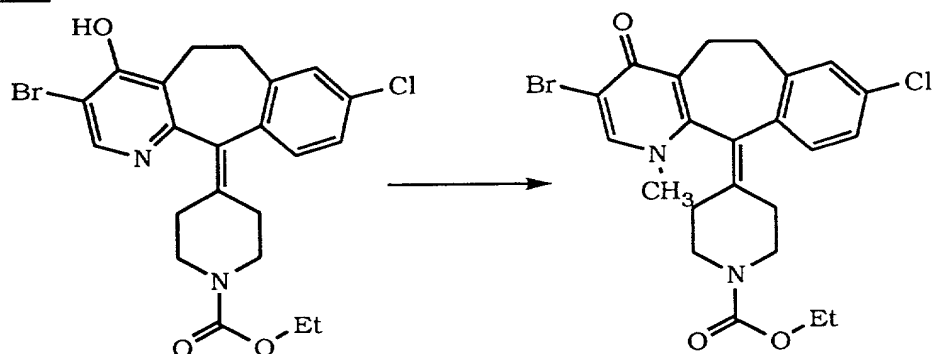
Combine 66 mg of the product compound from Preparative Example 56, Step B, 4 mL of anhydrous EtOH, and 15 mL of concentrated HCl stir at reflux for 60 hours. Cool the reaction mixture to about 0°C and basify by the adding KOH. Extract with CH<sub>2</sub>Cl<sub>2</sub>, dry the extract over MgSO<sub>4</sub>, and concentrate *in vacuo* to give 46 mg (81% yield) of the product compound. Mass Spec.: MH<sup>+</sup> = 462

15

PREPARATIVE EXAMPLE 57

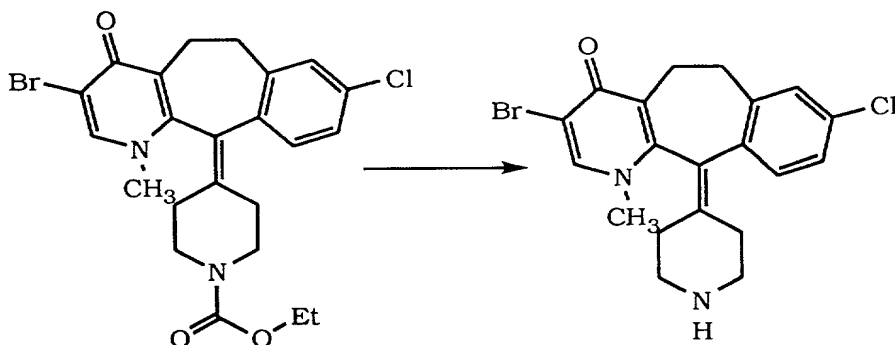


Step A:



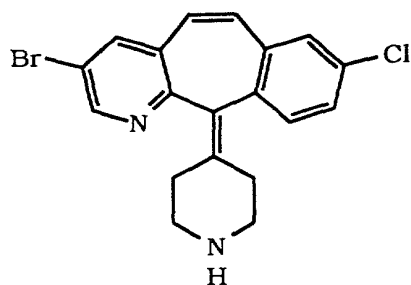
- 5        Combine 1.19 g of the product of Preparative Example 44, 10 mL of anhydrous DMF, 0.2 g of NaH (60% in mineral oil) and 0.19 mL of methyl iodide, and stir at room temperature overnight. Concentrate *in vacuo* to a residue, dilute the residue with CH<sub>2</sub>Cl<sub>2</sub>, wash with saturated NaHCO<sub>3</sub> (aqueous), and dry over MgSO<sub>4</sub>. Concentrate *in vacuo* to give 1.13 g  
10        (92% yield) of the product compound. Mass Spec.: MH<sup>+</sup> = 493.

Step B:

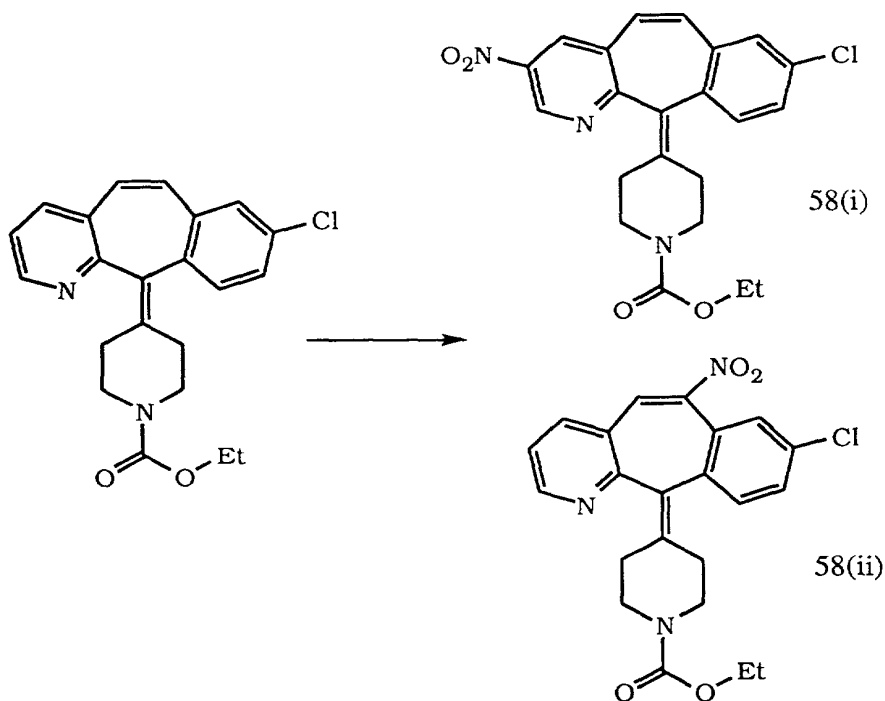


- 15        Hydrolyze 1.13 g of the product of Step A via substantially the same procedure as describe for Preparative Example 56, Step C, to give 0.61 g (63% yield) of the product compound.

PREPARATIVE EXAMPLE 58



Step A:

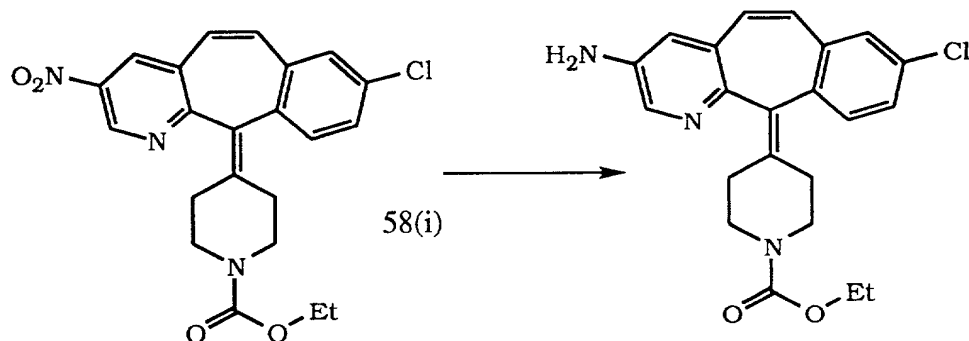


- 5            Combine 1.07 g (3.52 mmol) of tetrabutylammonium nitrate, 4 mL of anhydrous  $\text{CH}_2\text{Cl}_2$  and 0.743 g (3.52 mmol) of TFAA, and add the resulting mixture to a solution of 1.22 g (3.20 mmol) of the title compound of Preparative Example 37 in 8 mL of anhydrous  $\text{CH}_2\text{Cl}_2$  at room temperature. Stir at room temperature overnight, then wash with 20 mL of saturated  $\text{NaHCO}_3$  (aqueous) and 20 mL of brine, and dry over  $\text{MgSO}_4$ .
- 10           Concentrate *in vacuo* and chromatograph the resulting residue (silica gel, EtOAc/hexane) to give 0.216 g of the product compound 58(i) and 0.27 g of the product compound 58(ii).

Analytical data for Compound 58(i): Mass Spec.  $\text{MH}^+ = 426$ .

- 15           Analytical data for Compound 58(i): m.p.  $97.5^\circ - 99.2^\circ\text{C}$ .

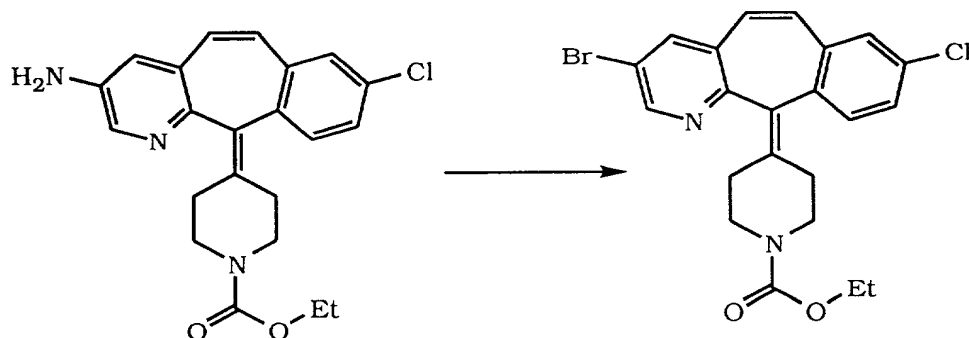
Step B:



Reduce the product 58(i) from Step A via essentially the same procedure as described in Preparative Example 47, Step B, to give the product compound. Mass Spec.:  $MH^+ = 396$

5

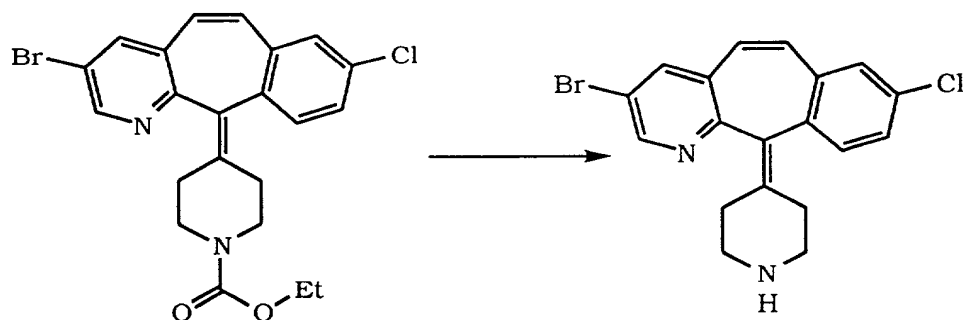
Step C:



React the product from Step B with HBr and bromine via essentially the same procedure as described in Preparative Example 47, Step C, to give the product compound. Mass Spec.:  $MH^+ = 459$

10

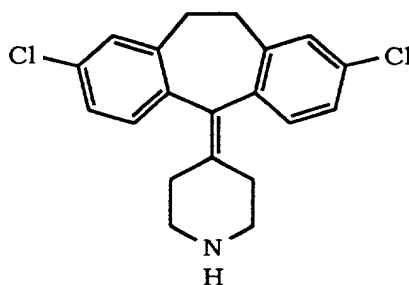
Step D:



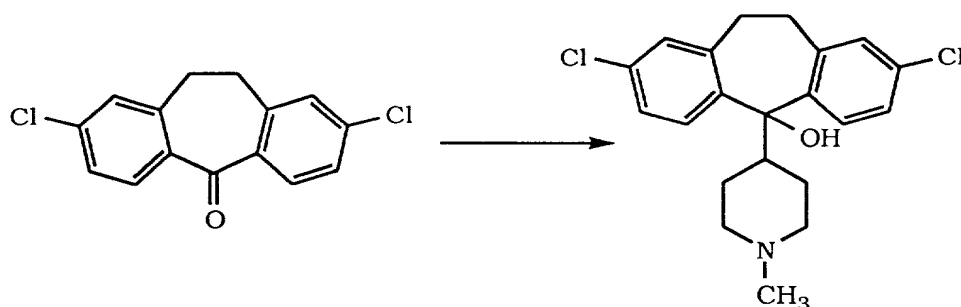
Hydrolyze 0.83 g of the product from Step C via essentially the same procedure as described in Preparative Example 56, Step C, to give 0.56 g of the product compound. Mass Spec.:  $MH^+ = 387$

15

**PREPARATIVE EXAMPLE 59**



**Step A:**

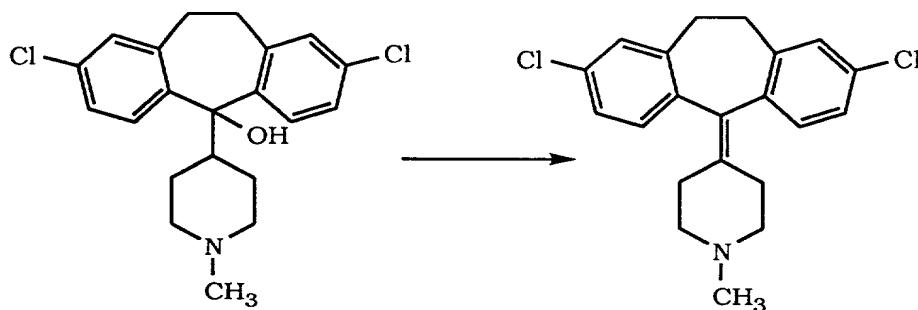


5

Combine 7.3 g (26.4 mmol) of the starting ketone (see J. Med. Chem., 4238 (1992)) and 230 mL of THF and cool to 0°C. Add a solution of 32.2 mmol of N-methyl-piperidine-4-magnesium bromide in 26 mL of THF and stir at 0°-5°C for 4 hours. Add 400 mL of EtOAc, wash with saturated NH<sub>4</sub>Cl (aqueous), and dry over MgSO<sub>4</sub>. Concentrate *in vacuo* to a residue, add ~200 mL of CH<sub>2</sub>Cl<sub>2</sub> and stir for 0.5 hours. Filter to collect the resulting solid and concentrate the filtrate to a volume of ~100 mL and let sit at 5 °C for 18 hours. Filter and combine the solids to obtain a total of 7 g (19.4 mmol) of the product compound. m.p.=153.7°-158 °C; Mass Spec.: (Cl) MH<sup>+</sup> = 376

10  
15

**Step B:**



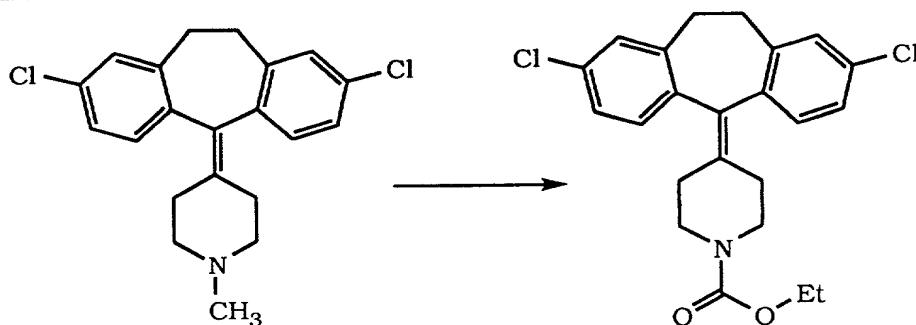
Combine 5 g of the product from Step A and 30 mL of TFA at ambient temperature and stir for 1 hour. Concentrate *in vacuo* to a

20



residue, dissolve the residue in  $\text{CH}_2\text{Cl}_2$  and wash with a saturated  $\text{NaHCO}_3$  (aqueous). Concentrate *in vacuo* to give 4.64 g of the product compound. m.p.=  $136.7^\circ\text{-}138^\circ\text{C}$ ; Mass Spec.: (FAB)  $\text{MH}^+ = 358.1$

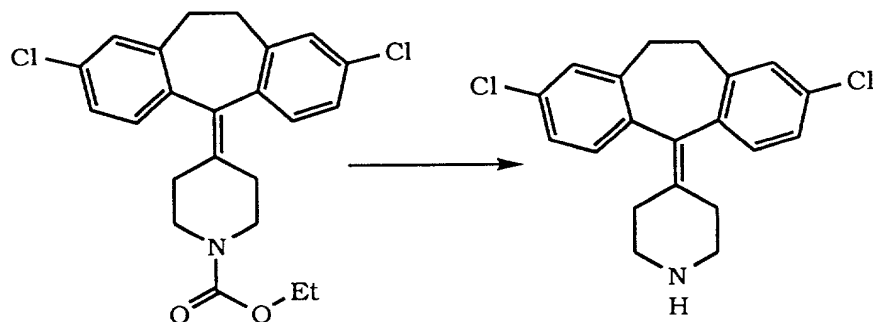
5 Step C:



Combine 0.6 g (1.75 mmol) of the product of Step B and 25 mL of toluene, add 0.73 mL (5.27 mmol) of  $\text{Et}_3\text{N}$  and 1.34 mL (14 mmol) of  $\text{ClCO}_2\text{Et}$ , and heat to  $80^\circ\text{C}$  for 2 hours. Add 0.7 mL more of  $\text{ClCO}_2\text{Et}$ , heat for 1 more hour, then cool to  $25^\circ\text{C}$  and concentrate *in vacuo* to a residue. Dissolve the residue in  $\text{EtOAc}$  and wash with 1N  $\text{NaOH}$  (aqueous) followed by brine. Dry over  $\text{MgSO}_4$ , concentrate *in vacuo* to a residue and chromatograph (silica gel, 10%  $\text{EtOAc}$ /hexanes) to give 0.55 g of the product compound. Mass Spec.: (FAB)  $\text{MH}^+ = 416.2$

15

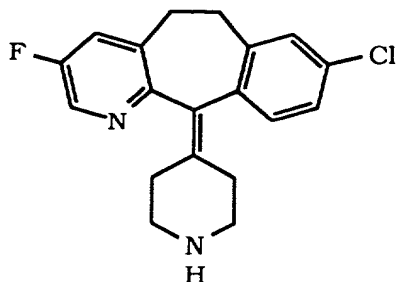
Step D:



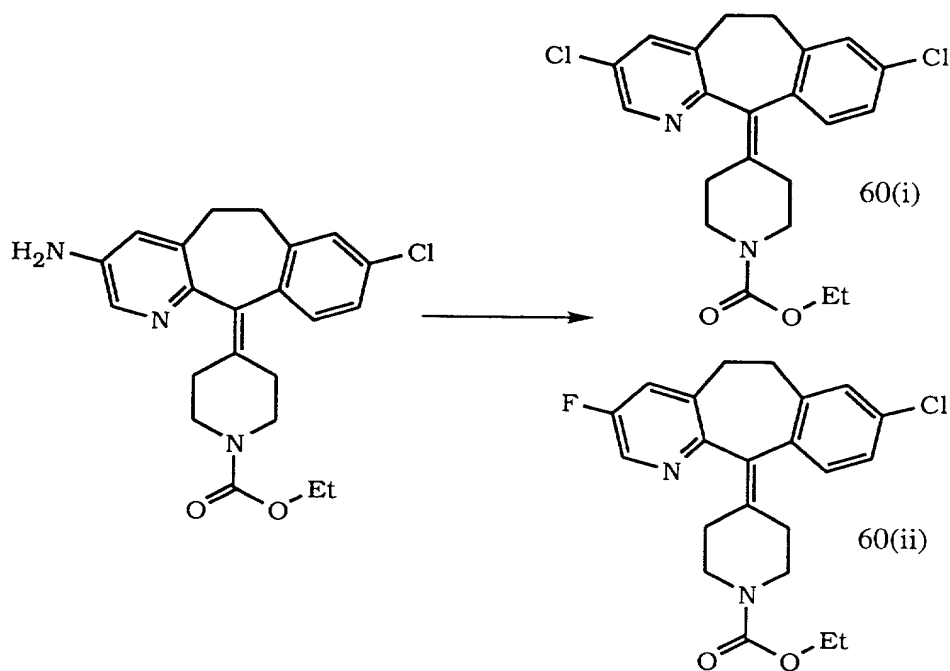
Dissolve 5 g (12.5 mmol) of the product of Step C in 30%  $\text{HBr}$  in  $\text{HOAc}$  and heat at  $40^\circ\text{C}$  for 24 hours, then cautiously add the mixture to cold 25 %  $\text{NaOH}$  (aqueous). Extract with  $\text{CH}_2\text{Cl}_2$  (3 X 100 mL), concentrate the extracts to a residue and chromatograph (silica gel, 5% to 30 %  $\text{MeOH}/\text{CH}_2\text{Cl}_2$ ) to give 2.18 g of the product compound. m.p.=  $159.5^\circ\text{-}160.8^\circ\text{C}$ ; Mass Spec.: (FAB)  $\text{MH}^+ = 344.1$

20

PREPARATIVE EXAMPLE 60

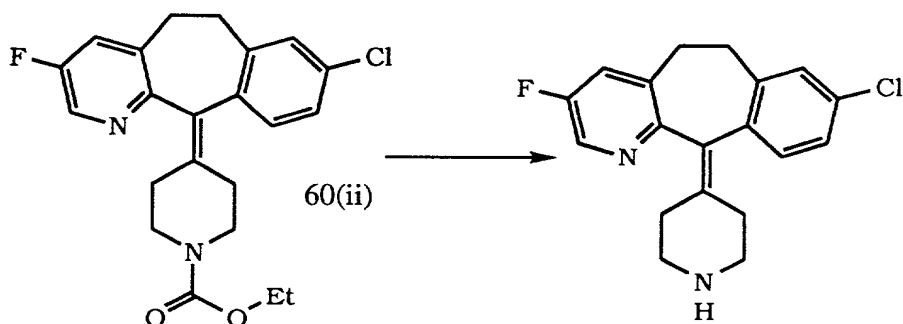


Step A:



- 5           Combine 16.25 g (40.83 mmol) of the product of Preparative Example 47, Step B, and a slurry of 7.14 g (61.11 mmol) of  $\text{NOBF}_4$  in 100 mL of  $\text{CH}_2\text{Cl}_2$  and stir the mixture for 3 hours. Add 100 mL of o-dichlorobenzene and heat for 5 hours, distilling the  $\text{CH}_2\text{Cl}_2$  from the mixture. Concentrate *in vacuo* to a residue, add 200 mL of  $\text{CH}_2\text{Cl}_2$  and
- 10       wash with water (2 X 200 mL). Dry over  $\text{MgSO}_4$ , concentrate *in vacuo* to a residue, and chromatograph (silica gel, 20% EtOAc/hexane) to give 4.1 g of product compound 60(i) and 4.01 g of Product compound 60(ii). Analytical data for compound 60 (i): Mass Spec.:  $\text{MH}^+ = 418$
- 15       Analytical data for compound 60 (ii): Mass Spec.:  $\text{MH}^+ = 401$

Step B:



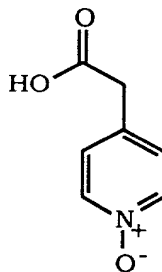
Hydrolyze 3.4 g of the product 60 (ii) from Step A via essentially the same process as described for Example 358, Step A, to give 3.01 g of product compound. Mass Spec.:  $MH^+ = 329$

- 5 Using the starting compound indicated and substantially the same procedure as described in Preparative Example 60, Step B, the following product compound is prepared:

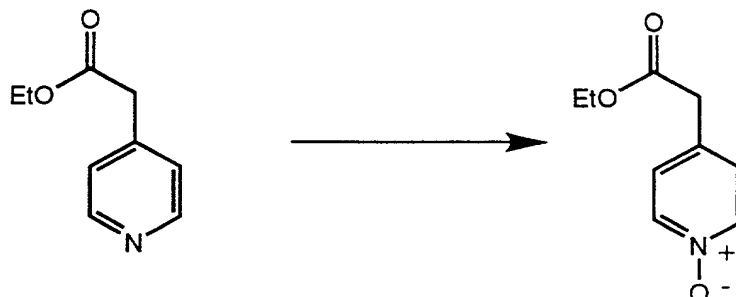
| Starting Compound                              | Compound   | Analytical Data             |
|--|--|-----------------------------|
| Preparative Example 60, Step A, compound 60(i) | <p style="text-align: center;">Preparative Example 60A</p> | Mass Spec.:<br>$MH^+ = 346$ |
|  |  |                             |

10

# PREPARATIVE EXAMPLE 61

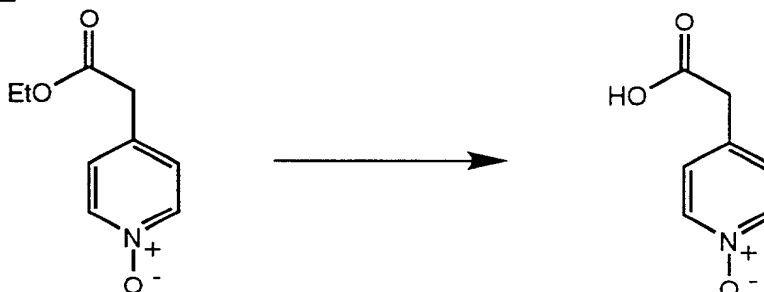


Step A:



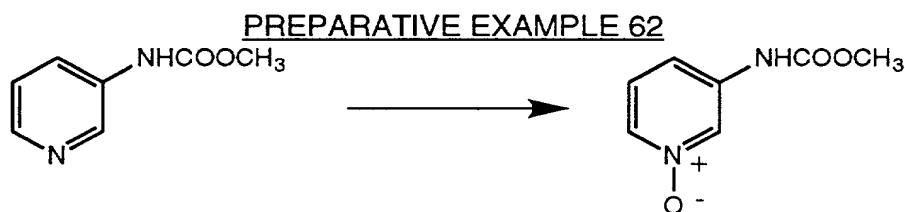
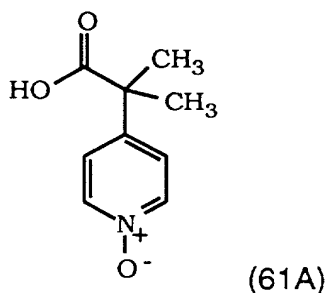
Combine 10 g (60.5 mmol) of ethyl 4-pyridylacetate and 120 mL of dry  $\text{CH}_2\text{Cl}_2$  at  $-20^\circ\text{C}$ , add 10.45 g (60.5 mmol) of MCPBA and stir at  $-20^\circ\text{C}$  for 1 hour and then at  $25^\circ\text{C}$  for 67 hours. Add an additional 3.48 g (20.2 mmol) of MCPBA and stir at  $25^\circ\text{C}$  for 24 hours. Dilute with  $\text{CH}_2\text{Cl}_2$  and wash with saturated  $\text{NaHCO}_3$  (aqueous) and then water. Dry over  $\text{MgSO}_4$ , concentrate *in vacuo* to a residue, and chromatograph (silica gel, 2%-5.5% (10%  $\text{NH}_4\text{OH}$  in  $\text{MeOH}$ )/ $\text{CH}_2\text{Cl}_2$ ) to give 8.12 g of the product compound. Mass Spec.:  $\text{MH}^+ = 182.15$

Step B:

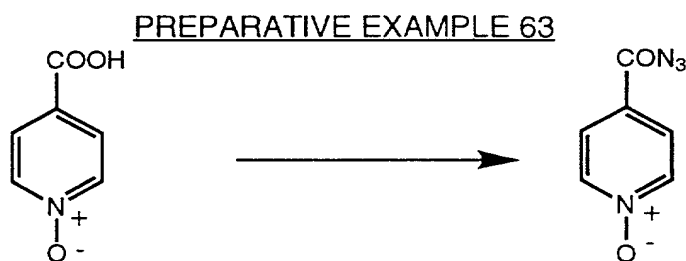


Combine 3.5 g (19.3 mmol) of the product of Step A, 17.5 mL of EtOH and 96.6 mL of 10% NaOH (aqueous) and heat the mixture at  $67^\circ\text{C}$  for 2 hours. Add 2 N HCl (aqueous) to adjust to pH = 2.37 and concentrate *in vacuo* to a residue. Add 200 mL of dry EtOH, filter through celite® and wash the filter cake with dry EtOH (2X50 ml). Concentrate the combined filtrates *in vacuo* to give 2.43 g of the title compound.

Using the product of Preparative Example 26 and substantially the same procedure as described for Preparative Example 61, Steps A and B, the following compound was prepared:

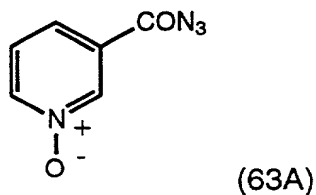


- 5            Combine 10 g (65.7 mmol) of 3-methoxycarbonylaminopyridine and 150 mL of CH<sub>2</sub>Cl<sub>2</sub>, cool to 0°C and slowly add (dropwise) a solution of 13.61 g (78.84 mmol) of MCPBA in 120 mL of CH<sub>2</sub>Cl<sub>2</sub> at 0°C over a period of 1 hour. Stir the mixture at 25°C for 5 days, then wash with saturated NaHCO<sub>3</sub> (aqueous), then water and dry over MgSO<sub>4</sub>.
- 10          Concentrate *in vacuo* to a residue and chromatograph (silica gel, 2%-5% (10% NH<sub>4</sub>OH in MeOH)/CH<sub>2</sub>Cl<sub>2</sub>) to give the product compound. Mass Spec.: MH<sup>+</sup> = 169



- 15            Combine 5 g (36.0 mmol) of isonicotinic acid 1-N-oxide and 150 mL of anhydrous DMF, add 5.5 mL (39.6 mmol) of Et<sub>3</sub>N and stir at 0°C for 0.5 hours. Slowly add (dropwise) 8.5 mL (39.6 mmol) of diphenylphosphoryl azide at 0°C over 10 minutes, stir at 0°C for 1 hour and then at 25°C for 24
- 20          hours (as generally described in Pavia, *et al.*, Journal of Medicinal Chemistry, **33**, 854-861 (1990). Concentrate *in vacuo* to a residue and chromatograph (silica gel, 0.5%-1% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to give 5.9 g of the product compound.

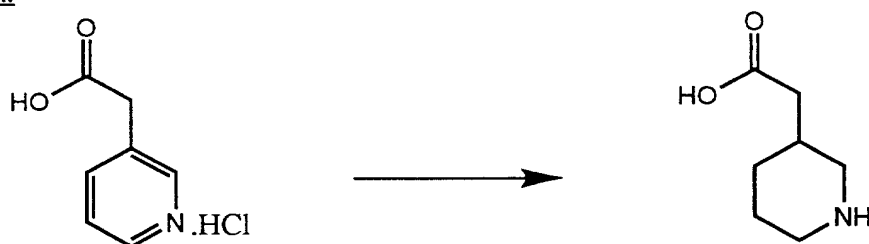
Using nicotinic acid 1-N-oxide and substantially the same procedure as described for Preparative Example 63 the following compound was prepared:



5

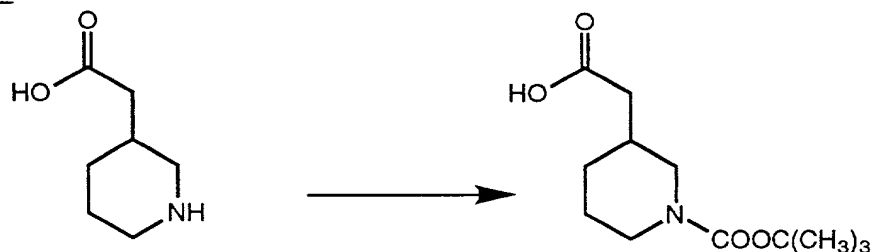
### PREPARATIVE EXAMPLE 64

#### Step A:



10 Hydrogenate 25 g (144 mmol) of 3-pyridylacetic acid hydrochloride for 144 hours using the procedure described in Preparative Example 15 to give 20 g of the product compound. Mass Spec.:  $MH^+ = 144$ .

#### Step B:

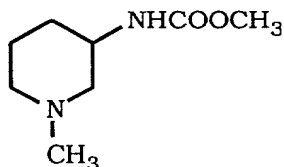


15

React 12 g (83.8 mmol) of the product of Step B for 148 hours using the procedure described in Preparative Example 13, Step B, to give 17.5 g of the product compound. Mass Spec.:  $MH^+ = 244.25$

20

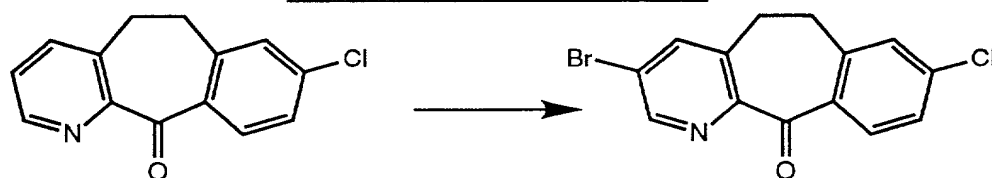
### PREPARATIVE EXAMPLE 65



Combine 25 g (164.4 mmol) of methyl 3-pyridylcarbamate and 163.3 mL of 1N HCl (aqueous), stir until all of the solid dissolves, then hydrogenate over 10% Pd/C at 25°C at 55 psi for 220 hours. Filter, wash the solids with water and treat the combined filtrates with 150 mL of  
 5 BioRad AG1X8 ion exchange resin (OH<sup>-</sup>). Filter, wash the resin with water and concentrate the filtrate to a volume of 100 mL. Add 16.43 mL (197.3 mmol) of 37% formalin and hydrogenate over 10% Pd/C at 25°C at 55 psi for 89 hours. Filter, wash the solids with water and concentrate *in vacuo* to give 24.3 g of the title compound. Mass Spec.: MH<sup>+</sup> = 173.2

10

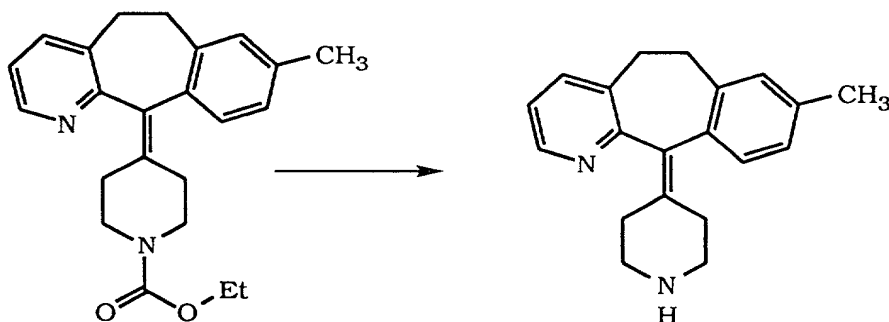
PREPARATIVE EXAMPLE 66



Cool 50.0 g (20.5 mmol) of 8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-one to 0°C, slowly add 75 mL  
 15 (93.69 mmol) of sulfur monochloride over 20 minutes, then slowly add 25 mL (48.59 mmol) of Br<sub>2</sub> over 15. Heat at 95°C for 20 hour, add 12.5 mL (24.3 mmol) of Br<sub>2</sub> and heat for a another 24 hours. Cool the mixture, and slowly add to a mixture of CH<sub>2</sub>Cl<sub>2</sub> and 1N NaOH (aqueous) at 0°C. Wash the organic phase with water, dry over MgSO<sub>4</sub> and concentrate *in vacuo*  
 20 to a residue. Chromatograph the residue (silica gel, 500 mL CH<sub>2</sub>Cl<sub>2</sub> then 0.2%-5% (10% NH<sub>4</sub>OH in MeOH)/CH<sub>2</sub>Cl<sub>2</sub>), then chromatograph again (silica gel, 3%-8.5% EtOAc/hexane) to give 8.66 g of the product compound. Mass Spec.: MH<sup>+</sup> = 322

25

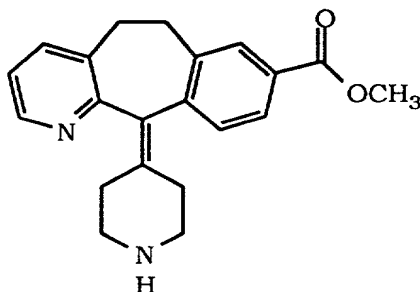
PREPARATIVE EXAMPLE 67



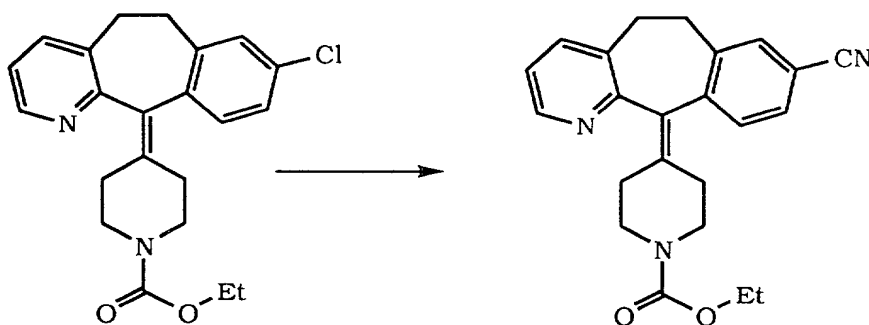
Dissolve 0.16 g (0.46 mmol) of 4-(8-methyl-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-1-ethoxycarbonyl-

piperidine, in 2 mL EtOH and add 4 mL of 12 N HCl. Heat the solution for 3 hours at 85°C, then cool to 25°C. Adjust to pH = 10 with 50% NaOH (aqueous) and extract several times with 50 mL of EtOAc. Combine the organic layers, dry them over MgSO<sub>4</sub>, and concentrate *in vacuo* to give the product compound.

PREPARATIVE EXAMPLE 68



Step A:



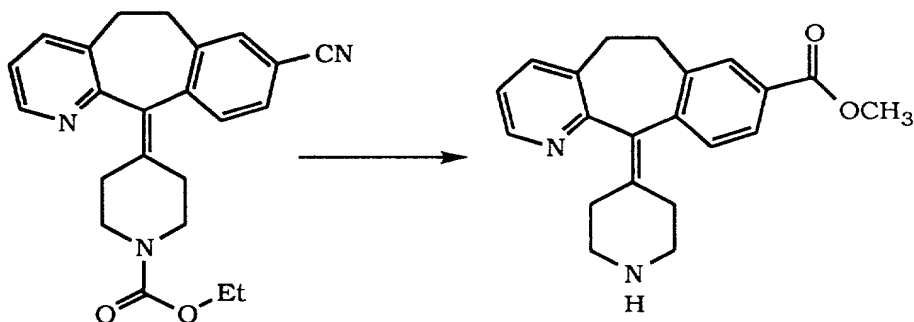
10

15 Dissolve 2 g (5.22 mmol) of the title compound of Preparative Example 1F in 2.6 mL of dry N-methyl-2-pyridone. Add 0.87 g (9.4 mmol) of CuCN and 0.139 g (0.93 mmol) of sodium iodide. Heat the mixture at 200° C under nitrogen for 20 hours, cool to 25° C and repeatedly grind and mix with five 50 mL portions of CH<sub>2</sub>Cl<sub>2</sub> and 7 M NH<sub>4</sub>OH (aqueous). Wash the organic layer with 7 M NH<sub>4</sub>OH until the organic layer is no longer blue or green. Dry the combined organic layers over MgSO<sub>4</sub> and concentrate *in vacuo* to a residue. Chromatograph (silica gel 70% EtOAc/hexane), then recrystallize from EtOAc/hexane to give the product compound. m.p. = 152.4°-153.5°C; Mass Spec.: MH<sup>+</sup> = 374

20



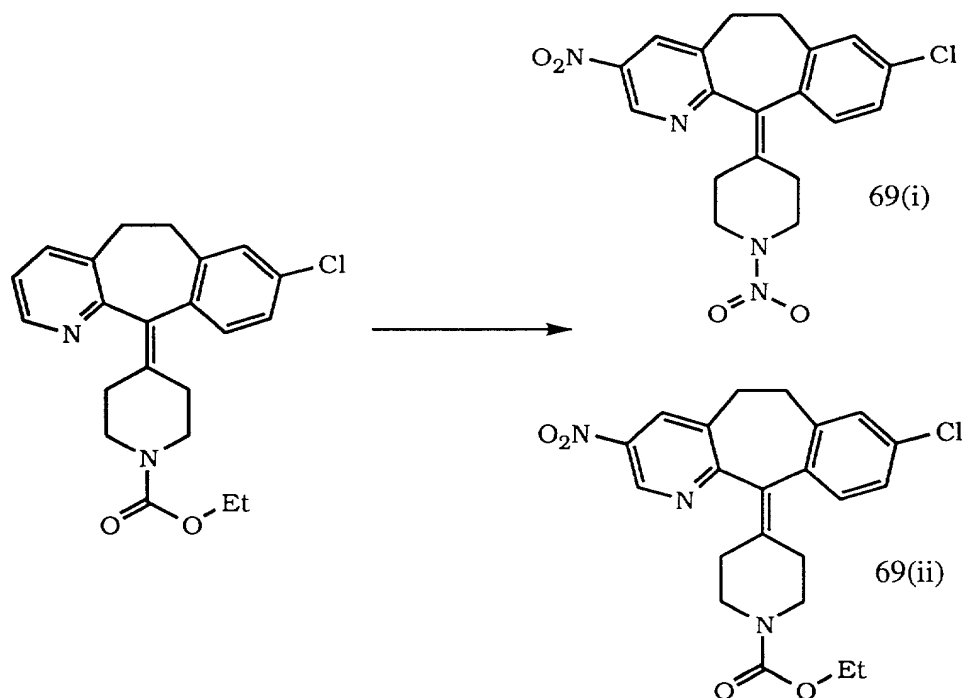
Step B:



Dissolve 4.08 g (10.93 mmol) of the product of Step A in 12 M HCl and heat at 85°C for 18 hours. Concentrate *in vacuo* to a residue.

- 5 Dissolve the residue in 175 mL of MeOH, saturate with HCl gas, and heat at reflux for 18 hours. Concentrate *in vacuo* to give the product compound as its HCl salt. Mass Spec.:  $MH^+ = 335$

PREPARATIVE EXAMPLE 68

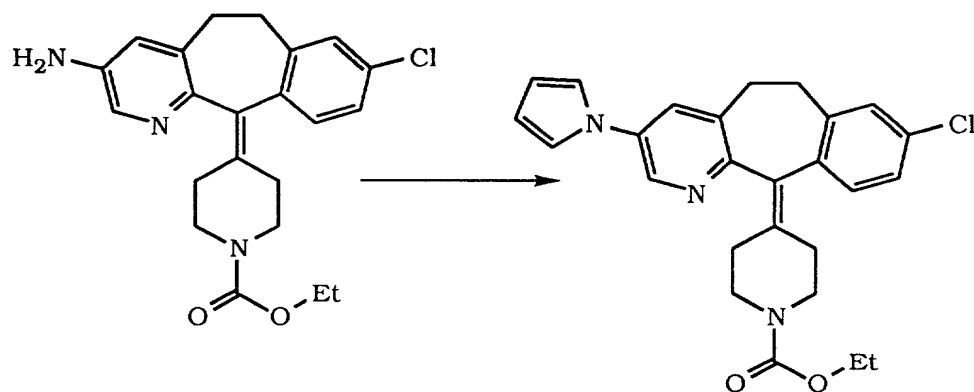


10

- 15 Combine 75 g (0.196 mole) of the Product of Example 1, Step F, and 300 mL of  $CH_2Cl_2$  at 0°C, and slowly add (dropwise) a solution of 72 g (0.236 mole) of tetrabutylammonium nitrate and 35 mL (0.247 mole) of TFAA in 500 mL of  $CH_2Cl_2$ . Stir at 25°C overnight, slowly add (dropwise) 1 L of saturated  $NaHCO_3$  (aqueous). Separate the layers, wash the

organic phase with brine and dry over  $\text{MgSO}_4$ . Concentrate *in vacuo* to a residue, chromatograph twice (1 kg silica gel, gradient of  $\text{EtOAc}/\text{CH}_2\text{Cl}_2$ ) to give 8.63 g of product compound 69(i), and 34 g of product compound (ii). Recrystallize compound 69(i) from  $\text{CH}_2\text{Cl}_2$ /hexane to give the purified product compound 69(i). m.p.=  $186^\circ\text{--}187^\circ\text{C}$ ; Mass Spec.: (FAB)  $\text{MH}^+ = 401$

#### PREPARATIVE EXAMPLE 69

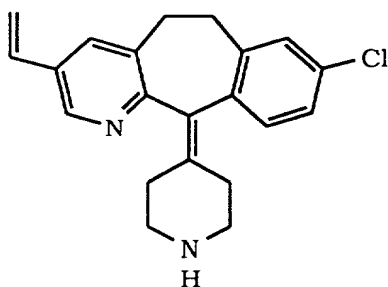


10

Combine 0.4 g (1 mmol) of the Product of Example 47, Step B, and 0.2 mL (1.2 mmol) of 2, 5-diethoxytetrahydrofuran in 3 mL of glacial  $\text{HOAc}$ , and heat at reflux for 1.5 hours. Cool the mixture, wash with saturated  $\text{NaHCO}_3$  (aqueous), then with brine, dry over  $\text{MgSO}_4$ , and concentrate *in vacuo* to a residue. Chromatograph (silica gel, 5%-15%  $\text{EtOAc}/\text{CH}_2\text{Cl}_2$ ) to give 0.34 g of the product compound. Mass Spec.: (FAB)  $\text{MH}^+ = 448$

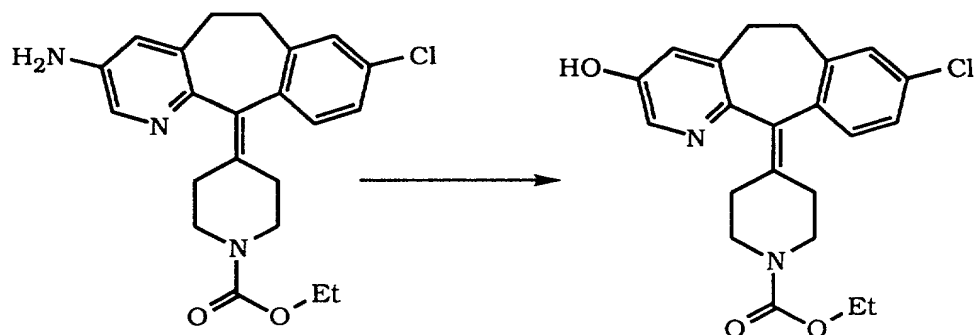
15

#### PREPARATIVE EXAMPLE 70



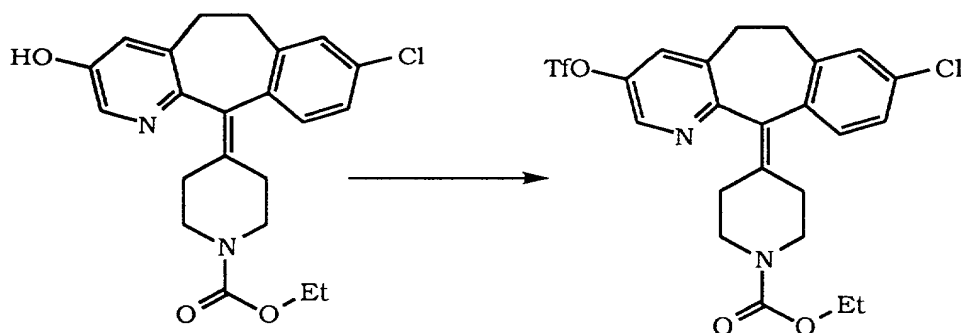
20

Step A:



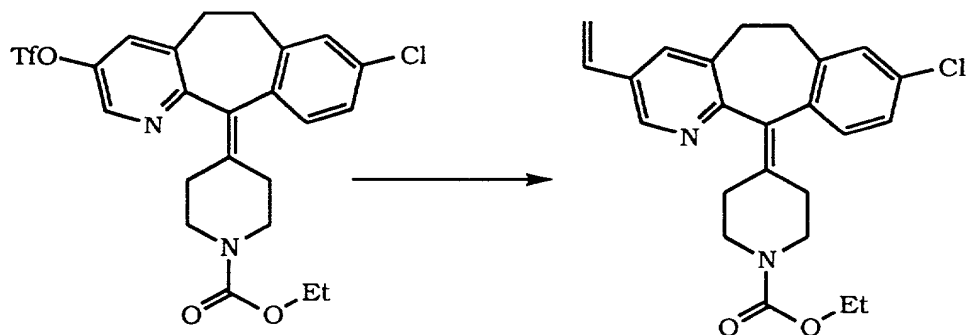
- Combine 13.8 g (34.7 mmol) of the Product of Example 47, Step B, and 90 mL of water at  $0^\circ\text{C}$ , add a solution of 6.9 mL of concentrated  $\text{H}_2\text{SO}_4$  in 45 mL of water and stir the mixture. Slowly add (dropwise) a solution of 2.55 g (40 mmol) of  $\text{NaNO}_2$  in 75 mL of water and stir at  $0^\circ\text{--}5^\circ\text{C}$  for 0.5 hours. Add a boiling solution of 35.1 g  $\text{CuSO}_4$  in 135 mL of water and heat at  $100^\circ\text{C}$  for 15 min. Cool the mixture, extract with  $\text{CH}_2\text{Cl}_2$  (2 X 200 mL), wash the extracts with brine, dry over  $\text{MgSO}_4$ , and concentrate *in vacuo* to a residue. Chromatograph (silica gel, 1.5%–10%  $\text{MeOH}/\text{CH}_2\text{Cl}_2$ ) to give 11.36 g of the product compound.

Step B:



- Combine 11.36 g (28.5 mmol) of the Product of Step A and 12.4 g (34.7 mmol) of N-phenyltriflimide in 120 mL of dry  $\text{CH}_2\text{Cl}_2$  at  $0^\circ\text{C}$ , add 4.6 mL (33 mmol) of  $\text{Et}_3\text{N}$  and stir at  $25^\circ\text{C}$  overnight. Concentrate *in vacuo* to a residue and chromatograph (silica gel, 2%–5%  $\text{EtOAc}/\text{CH}_2\text{Cl}_2$ ) to give 10.95 g of the product compound. Recrystallize from hot  $\text{MeOH}$ . m.p. =  $154.5^\circ\text{--}156^\circ\text{C}$ ; Mass Spec.: (FAB)  $\text{MH}^+ = 531$

Step C:

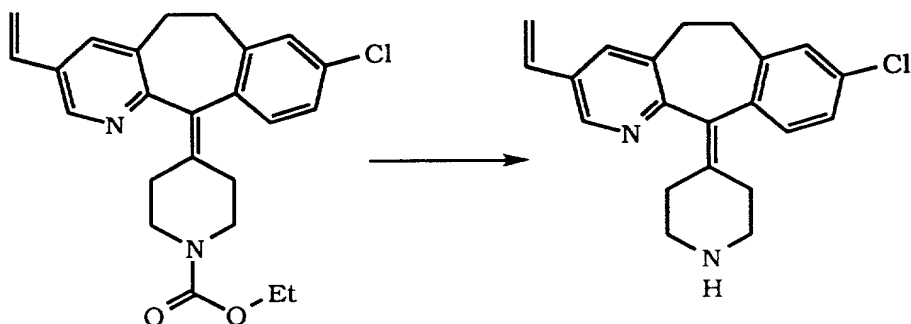


Combine 12.2 g (23 mmol) of the Product of Step B and 85 mL of 1-methyl-2-pyrrolidinone at 25°C, then add 2.84 g LiCl, 0.212 g of tris-furylphosphine and 0.585 g of dipalladiumtribenzylideneacetone and stir for 15 min. Slowly add (dropwise) 7.5 mL (25.77 mmol) of tributylvinyltin and stir at 25°C for 2.5 hours. Dilute with 500 mL of water at 0°C and extract with 6700 mL of EtOAc. Filter the organic phase through celite®, wash the celite with EtOAc, then wash the filtrate twice with 30% NaF (aqueous). Filter the organic solution wash with brine and dry over MgSO<sub>4</sub>. Concentrate *in vacuo* to a residue and chromatograph (silica gel, 15%-40% EtOAc/hexane) to give 8.58 g of the product compound. Mass Spec.: (FAB) MH<sup>+</sup> = 409

Using the stannane indicated, the following compounds were prepared via substantially the same procedure as described for Preparative Example 70, Step C:

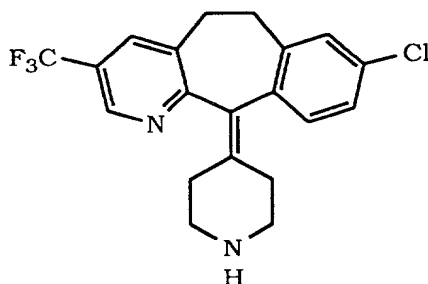
| Starting Compound   | Product Compound                | Analytical Data  |
|---|---------------------------------|--|
| 2-(tributylstannyl)-thiophene and Preparative Example 70 Step B | <p>Preparative Example 70-A</p> | <p>m.p. = 155°~157°C</p> <p>Mass Spec.: MH<sup>+</sup> = 465</p> |
|   |                                 |  |

Step D:

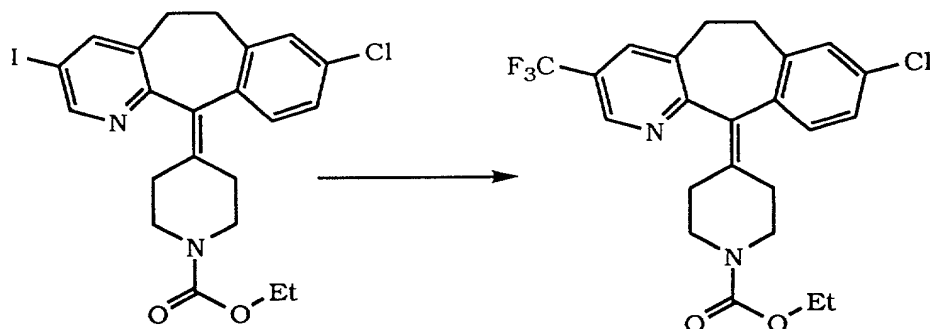


Hydrolyze 1.18 g (2.89 mmol) of the product of Step C via substantially the same procedure as described in Example 358, Step A, to give 0.95 g of the product compound. Mass Spec.: (FAB)  $MH^+ = 337$

#### PREPARATIVE EXAMPLE 71



Step A:

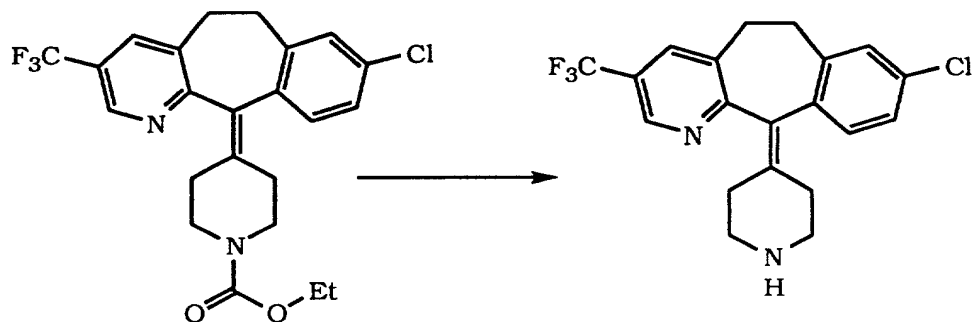


10

Combine 1.01 g (19.9 mmol) of the Product of Example 48, Step A, 30 mL of DMF, 1.33 g (6.96 mmol) of methyl 2,2-difluoro-2-(fluorosulfonyl)-acetate and 0.75 g (3.97 g) of CuI. Heat the mixture at 60°-80°C for 3 hours, then concentrate to a residue. Dilute the residue with water, extract with CH<sub>2</sub>Cl<sub>2</sub>, and concentrate *in vacuo* to a residue. Chromatograph (silica gel, 30% EtOAc/hexane, then 10% MeOH/CH<sub>2</sub>Cl<sub>2</sub> + NH<sub>4</sub>OH) to give 0.15 g of the product compound. Mass Spec.:  $MH^+ = 451.1$

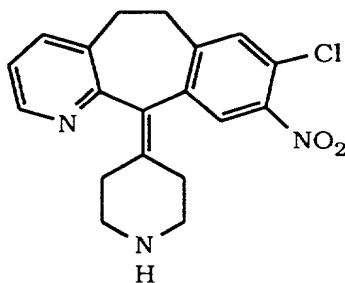
15

Step B:

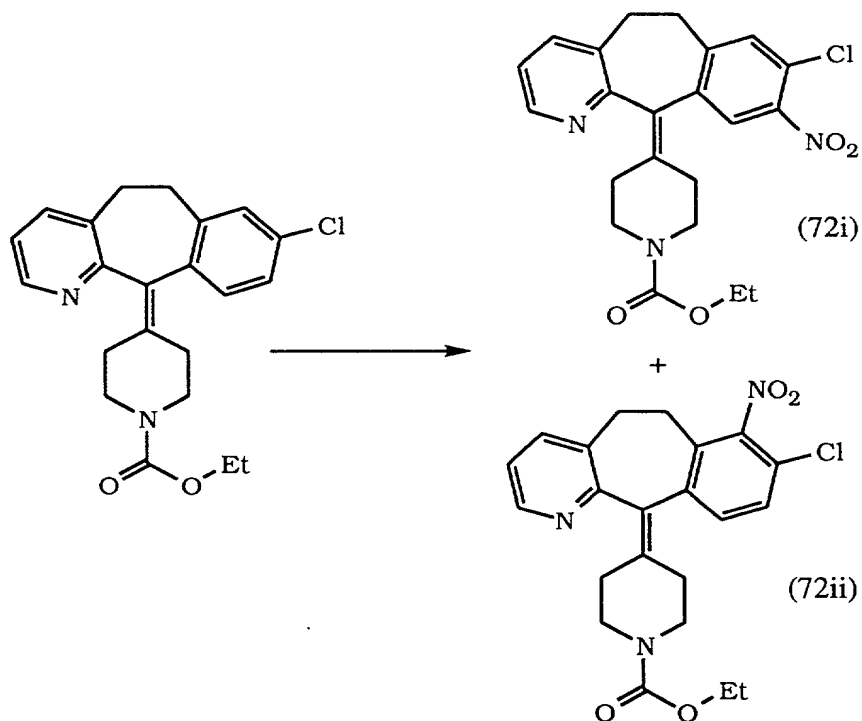


Hydrolyze the product of Step A using essentially the same procedure as described in Preparative Example 1, Step G, to give the product compound. Mass Spec.:  $\text{MH}^+ = 379$

PREPARATIVE EXAMPLE 72



Step A:

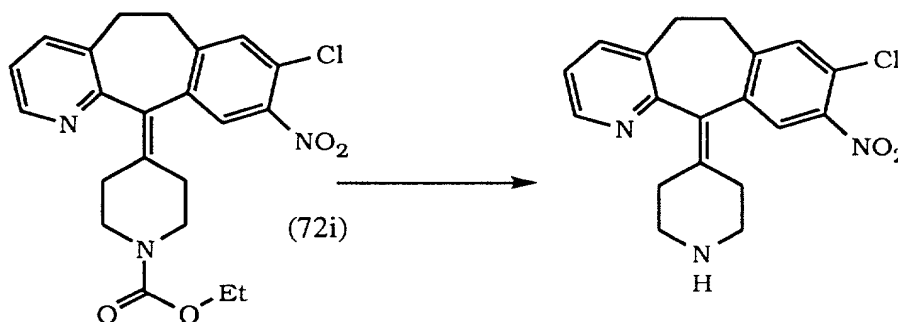


Dissolve 20 g (50 mmol) of the Product of Example 1, Step F, in 400 mL of concentrated  $\text{H}_2\text{SO}_4$ , cool to  $-5^\circ\text{C}$  and add 5.1 g (50 mmol) of  $\text{KNO}_3$  in small portions. Stir for 3 hours, cool the mixture and slowly basify with 50%  $\text{NaOH}$  (aqueous). Extract with  $\text{CH}_2\text{Cl}_2$  (3 X 500 mL), dry the combined extracts over  $\text{MgSO}_4$ , and concentrate *in vacuo* to a residue. Chromatograph (silica gel, 50%  $\text{EtOAc}$ /hexane) to give 16.33 g of the product compound (72i) and 2.6 g of the product compound (72ii).

For product compound (72i), Mass Spec.:  $\text{MH}^+ = 428$ .

For product compound (72ii), Mass Spec.:  $\text{MH}^+ = 428$ .

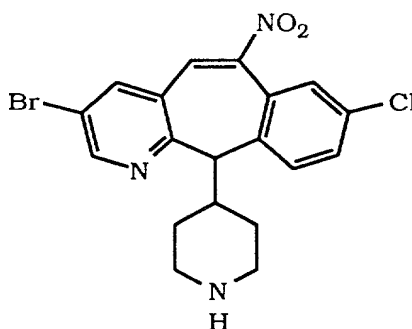
Step B:



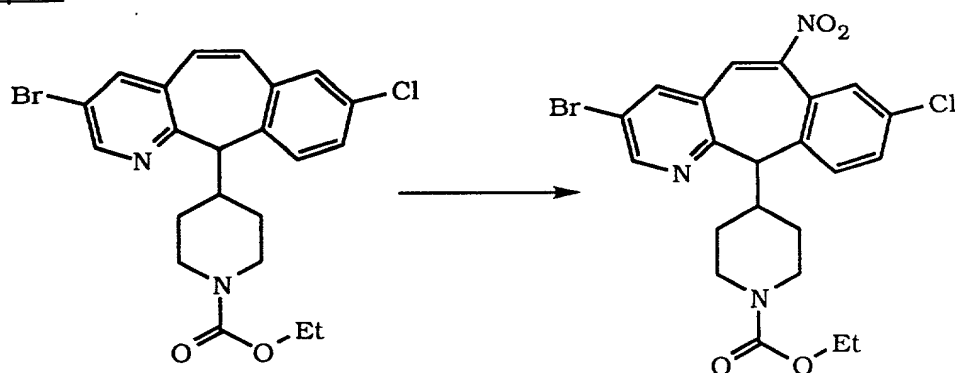
Hydrolyze 5.46 g (12.76 mmol) of the Product of (72i) from Step A, via substantially the same procedure as described for Example 358, Step

A, to give 4.34 g of the product compound. Mass Spec.:  $\text{MH}^+ = 356$

PREPARATIVE EXAMPLE 73



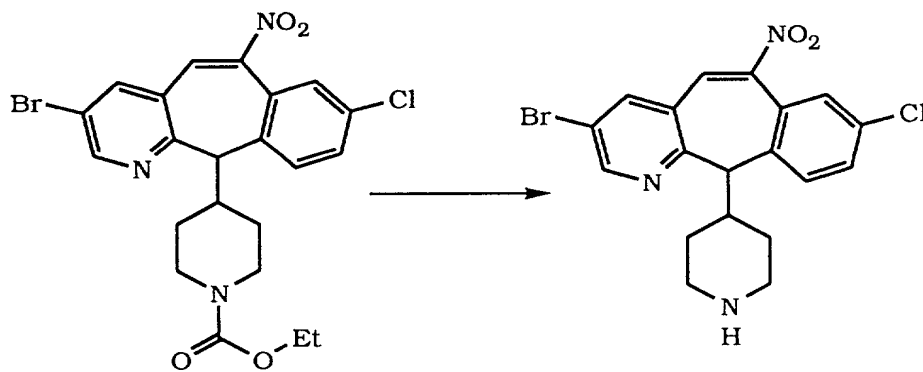
Step A:



Combine 1.6 g of the Product (54i) of Preparative Example 54, Step B, 12 mL of CH<sub>2</sub>Cl<sub>2</sub>, and 1.16 g of tetrabutylammonium nitrate, cool to 0°C and slowly add (dropwise) a solution of 0.8 g of TFAA in 2 mL of CH<sub>2</sub>Cl<sub>2</sub>. Stir for 6 hours at 0°C, let the mixture stand at 0°C overnight, then wash successively with saturated NaHCO<sub>3</sub> (aqueous), water and brine, and dry over Na<sub>2</sub>SO<sub>4</sub>. Concentrate *in vacuo* to a residue, then chromatograph (silica gel, 30% EtOAc/hexane) to give 0.38 g of the product compound.

10

Step B:



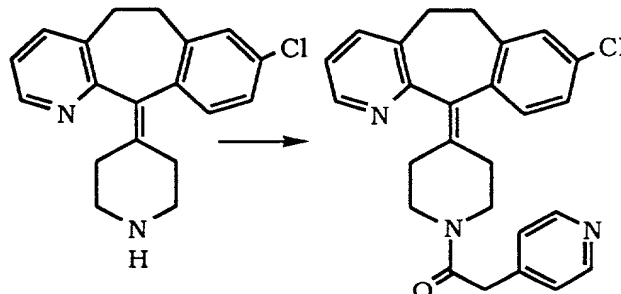
Hydrolyze 0.38 g of the Product of Step A via substantially the same procedure as described for Example 358, Step A, to give 0.235 g of the product compound.

15



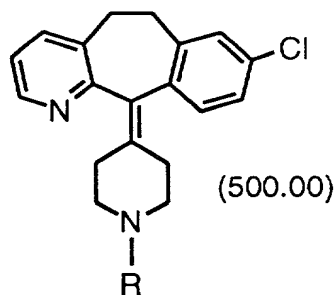
EXAMPLE 1

1-(4-PYRIDYLACETYL)-4-(8-CHLORO-5,6-DIHYDRO-11H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11-YLIDENE)PIPERIDINE



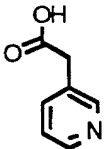
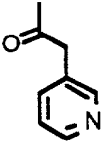
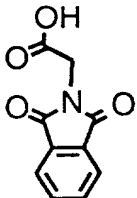
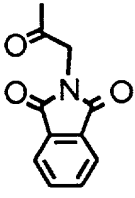
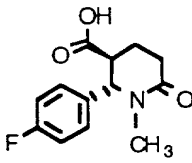
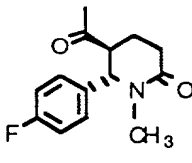
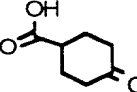
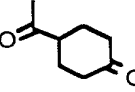
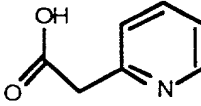
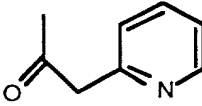
- 5 To a mixture of 528 mg (1.7 mmol) of 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)piperidine (product from Preparative Example 1, Step G), 274 mg (1.7 mmol) of 4-pyridylacetic acid hydrochloride, and 242 mg (1.8 mmol) of HOBt in 5 mL of dry CH<sub>2</sub>Cl<sub>2</sub> at -15 °C and under a nitrogen atmosphere was added dropwise 0.17 mL
- 10 (1.5 mmol) of Et<sub>3</sub>N followed by a solution of 363 mg (1.9 mmol) of DEC in 5 mL of dry CH<sub>2</sub>Cl<sub>2</sub>. The reaction mixture was slowly allowed to warm to room temperature. After 4 hours the mixture was poured into water and extracted several times with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic portions were dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo* to give a
- 15 product which was purified via flash chromatography (3% MeOH saturated with ammonia in CH<sub>2</sub>Cl<sub>2</sub>) 155 mg of 1-(4-pyridylacetyl)-4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)piperidine as a solid: mp 152 - 155 °C.

- 20 By essentially the same procedure as set forth in Example 1, but using the carboxylic acids set forth in column 1, of Table 2 below, in place of 4-pyridylacetic acid, one can obtain the compounds listed in column 2 of Table 2. The compounds listed in Table 2 refer to compounds of Formula 500.00:



- 25 wherein R is the substituent in Column 2.

TABLE 2

| EXAMPLE | COLUMN 1  | COLUMN 2   | COMPOUND                   |
|---------|---|--|----------------------------|
| 2       |    |    | glass                      |
| 3       |    |    | white powder               |
| 4       |    |    | white solid                |
| 5       |   |   | white crystals<br>mp 200°C |
| 6       |  |  | mp<br>122 - 125°C          |

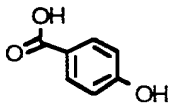
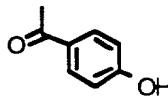
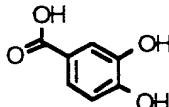
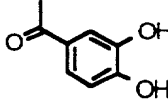
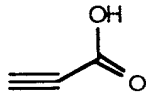
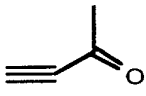
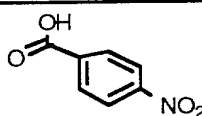
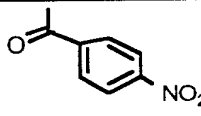
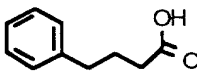
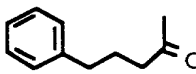
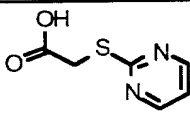
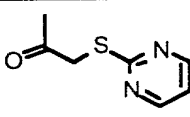
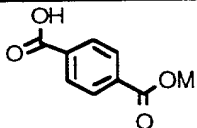
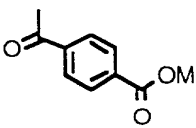
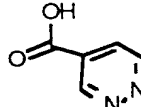
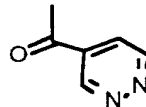
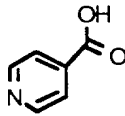
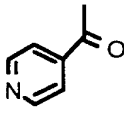
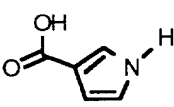
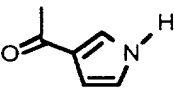
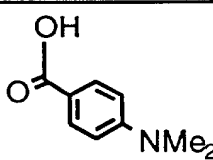
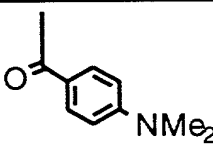
| EXAMPLE | COLUMN 1  | COLUMN 2   | COMPOUND            |
|---------|---|--|---------------------|
| 7       |    |    | ----                |
| 8       |    |    | off<br>white powder |
| 9       |    |    | glass               |
| 10      |    |    | white solid         |
| 11      |    |    | white solid         |
| 12      |  |  | glass               |
| 13      |  |  | white solid         |
| 14      |  |  | glass               |
| 15      |  |  | mp<br>176 - 178°C   |
| 16      |  |  | glass               |
| 17      |  |  | mp<br>200 -204°C    |

TABLE 2 - continued

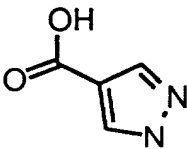
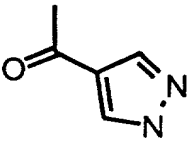
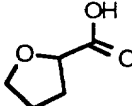
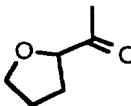
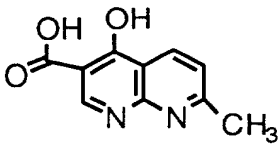
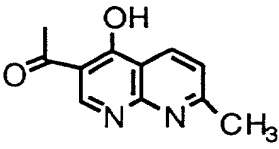
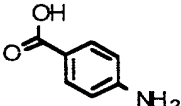
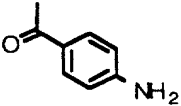
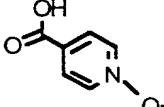
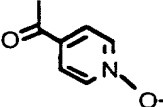
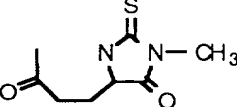
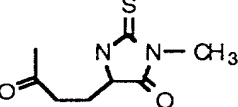
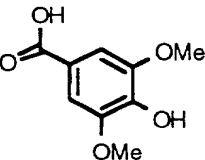
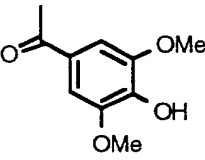
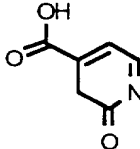
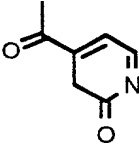
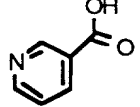
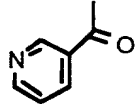
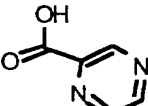
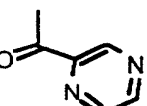
| EXAMPLE | COLUMN 1  | COLUMN 2   | COMPOUND                      |
|---------|---|--|-------------------------------|
| 18      |    |    | glass                         |
| 19      |    |    | glass                         |
| 20      |    |    | yellow solid                  |
| 21      |   |   | off white solid               |
| 22      |  |  | white solid<br>mp 228°C (dec) |
| 23      |  |  | white solid<br>mp 205-207°C   |
| 24      |  |  | white powder                  |
| 25      |  |  | white powder                  |
| 26      |  |  | glass                         |
| 27      |  |  | glass                         |

TABLE 2 continued

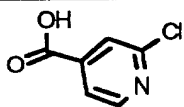
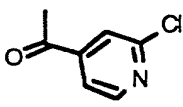
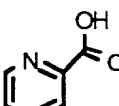
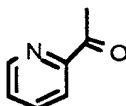
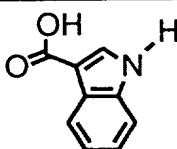
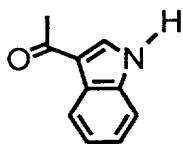
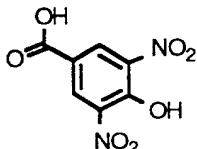
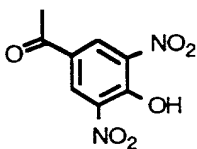
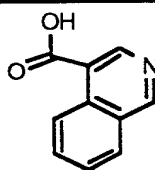
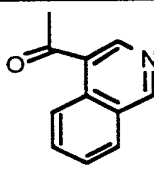
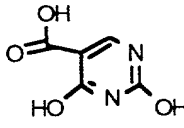
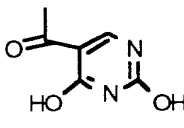
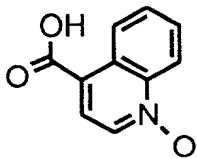
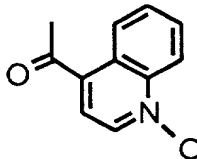
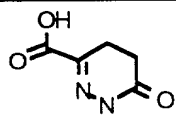
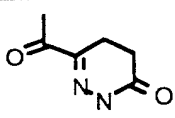
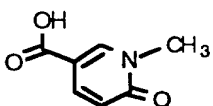
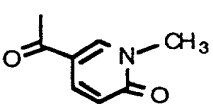
| EXAMPLE | COLUMN 1  | COLUMN 2   | COMPOUND                   |
|---------|---|--|----------------------------|
| 28      |    |    | glass                      |
| 29      |    |    | glass                      |
| 30      |    |    | mp<br>211 - 215°C          |
| 31      |    |    | yellow solid               |
| 32      |  |  | white solid                |
| 33      |  |  | white solid                |
| 34      |  |  | glass                      |
| 35      |  |  | solid<br>mp<br>190 - 193°C |
| 36      |  |  | solid                      |

TABLE 2 - continued

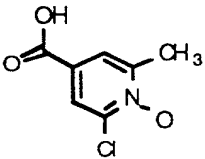
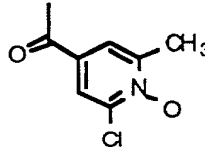
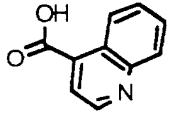
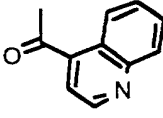
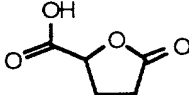
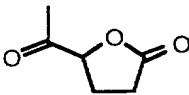
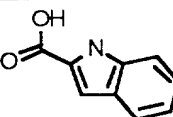
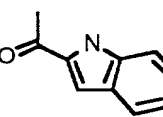
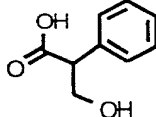
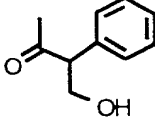
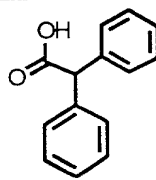
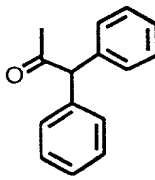
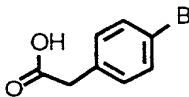
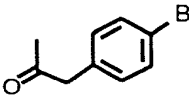
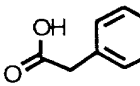
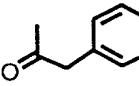
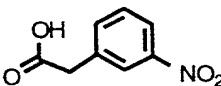
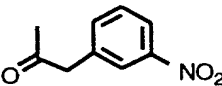
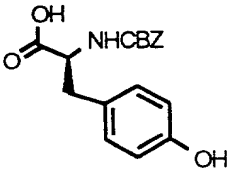
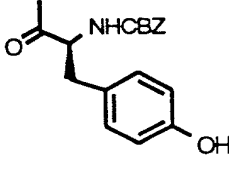
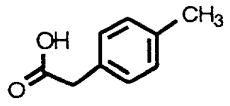
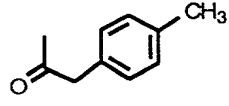
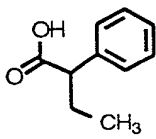
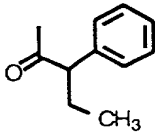
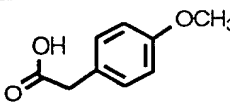
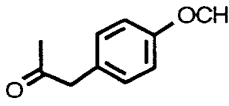
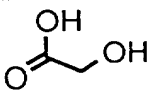
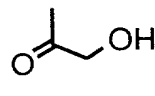
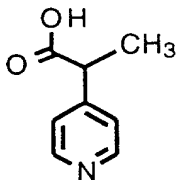
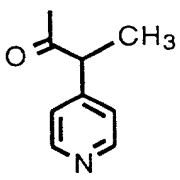
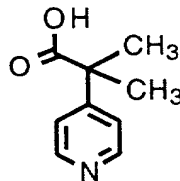
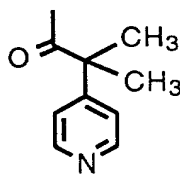
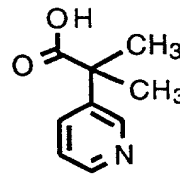
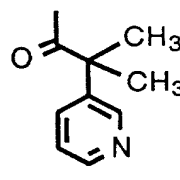
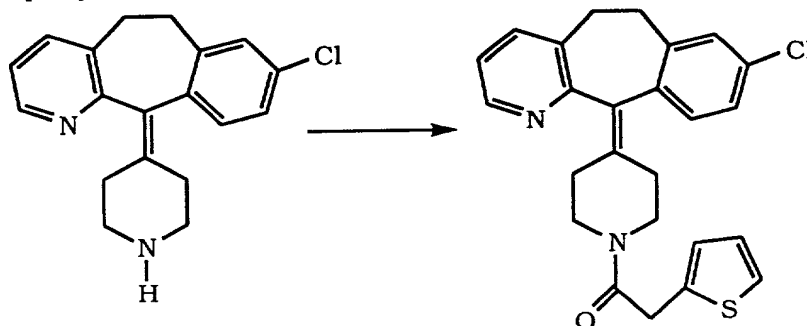
| EXAMPLE | COLUMN 1  | COLUMN 2   | COMPOUND  |
|---------|---|--|---|
| 37      |    |    | glass   |
| 38      |    |    | white solid   |
| 39      |    |    | glass   |
| 40      |    |    | mp<br>218 - 220°C                                       |
| 41      |   |   | light brown solid<br>mp =<br>92.7 - 93°C<br>MS M+ = 459 |
| 42      |  |  | white solid<br>mp =<br>114.2 - 115.8°C<br>MS M+ = 506   |
| 43      |  |  | white solid<br>mp =<br>93.3 - 94.6°C<br>MS M+ = 506     |
| 44      |  |  | white solid<br>mp =<br>112 - 114.6°C<br>MS M+ = 428     |
| 45      |  |  | white solid<br>mp =<br>94.3 - 95.5°C<br>MS M+ = 474     |

TABLE 2 - continued

| EXAMPLE | COLUMN 1  | COLUMN 2   | COMPOUND  |
|---------|---|--|---|
| 46      |                          |    | white solid<br>mp =<br>126.5 - 127.5°C<br>MS M+ = 607 |
| 47      |                          |    | white solid<br>mp =<br>83.6 - 85.0°C                  |
| 48      |                          |    | white solid<br>mp =<br>82.7 - 83.8°C<br>MS M+ = 456   |
| 49      |                         |   | white solid<br>MS M+ = 534                            |
| 49a     |                        |  | white solid<br>mp =<br>73.5 - 73.8°C                  |
| 288     | <br>Preparative Ex. 25 |  | white solid<br>MH+ 452                                |
| 299     | <br>Preparative Ex. 26 |  | off white solid<br>MH+ 459                            |
| 300     | <br>Preparative Ex. 10 |  | white solid<br>MH+ 459                                |

EXAMPLE 50

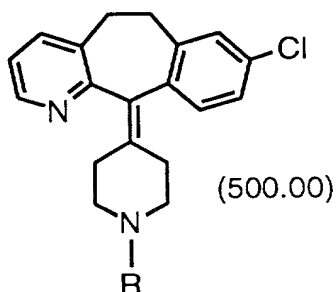
1-(2-THIOPHENEACETYL)-4-(8-CHLORO-5,6-DIHYDRO-11H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11-YLIDENE)PIPERIDINE



- 5 To a solution of 1.0 gm (3.22 mmole) of 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta [1,2-b] pyridin-11-ylidene) piperidine and 0.29 mL of pyridine in 20 mL of dry CH<sub>2</sub>Cl<sub>2</sub> at 0°C and under an argon atmosphere was added dropwise 0.438 mL (3.55 mmol) of 2-
- 10 thiopheneacetyl chloride. After 30 minutes the mixture was washed with 1.0 N aqueous NaOH and then brine. The organic portion was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and converted in vacuo to provide a residue which was purified via flash chromatography (3% MeOH in CH<sub>2</sub>Cl<sub>2</sub>) and treated with activated carbon to provide the title compound as a glass.

15 EXAMPLE 51

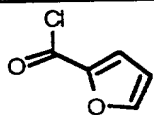
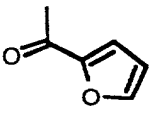
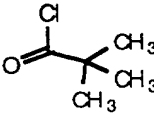
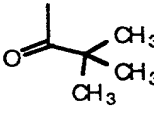
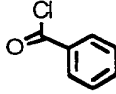
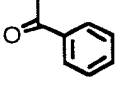
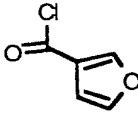
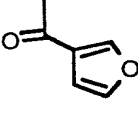
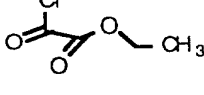
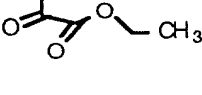
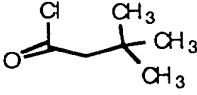
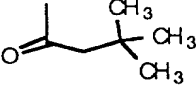
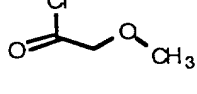
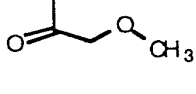
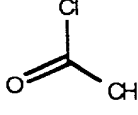
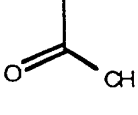
- By essentially the same procedure as set forth in Example 50, but using the acid chlorides set forth in Column 1, in Table 3 below, in place of 2-thiopheneacetyl chloride, one can obtain the compounds listed in Column 2 of Table 3. The compounds listed in Table 3 refer to
- 20 compounds of Formula 500.00:



wherein R is the substituent in Column 2

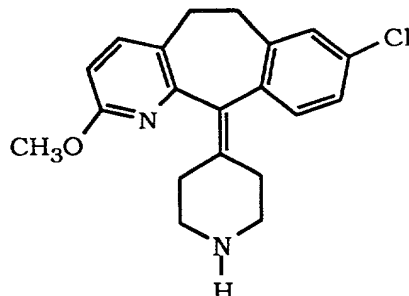


TABLE 3

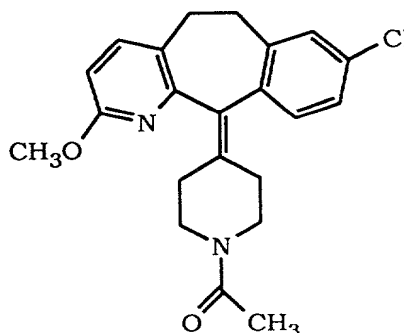
| EXAMPLE | COLUMN 1  | COLUMN 2   | COMPOUND                         |
|---------|---|--|----------------------------------|
| 52      |    |    | solid                            |
| 53      |    |    | solid<br>mp<br>158 - 160°C       |
| 54      |    |    | glass                            |
| 55      |    |    | white powder                     |
| 56      |  |  | solid<br>mp<br>126 - 128°C       |
| 57      |  |  | solid<br>mp<br>137 - 139°C       |
| 58      |  |  | solid<br>mp<br>104 - 106°C       |
| 59      |  |  | white solid<br>mp<br>155 - 157°C |

EXAMPLE 65

By essentially the same procedures as set forth in Example 50 above, or Example 4 of US 5,089,496, but using



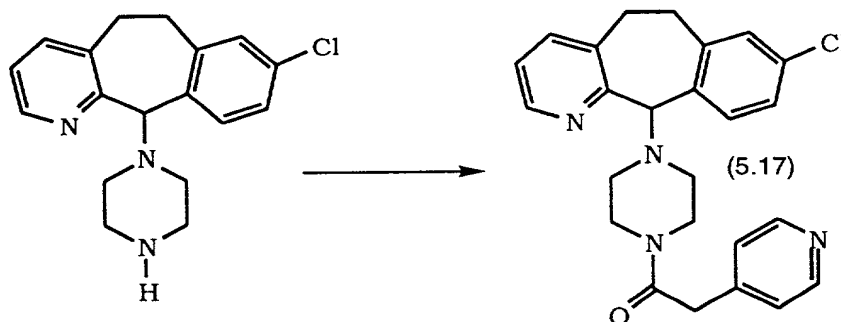
- 5 in place of 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)piperidine, one can obtain the compound



as a white solid.

EXAMPLE 75

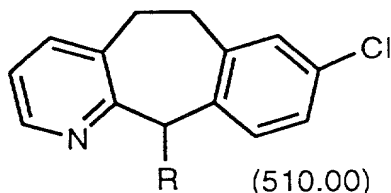
10 1-(8-CHLORO-5,6-DIHYDRO-11H-BENZO[5,6]CYCLO-HEPTA[1,2-b]PYRIDIN-11-YL-4-(4-PYRIDYLACETYL)-PIPERAZINE



- 15 To a mixture of 8.5 g (27.2 m mole) of 8-chloro-11-(1-piperazinyl)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine (Preparative Example 7) in 256 mL of anhydrous DMF at room temperature and under an argon atmosphere was added 2.98 g (27.2 m mole) of 4-methylmorpholine, 7.81 g (27.2 m mole) of DEC, 3.68 g (27.2 m mole) of HOBT,

- and 3.72 g (27.2 m mole) of 4-pyridylacetic acid. The mixture was stirred at room temperature for 22 hours. The mixture was poured into 3300 mL of  $\text{CH}_2\text{Cl}_2$  and washed with 500 mL of water. The aqueous layer was extracted with 500 mL of  $\text{CH}_2\text{Cl}_2$ . The combined organic portions were dried over  $\text{MgSO}_4$ , filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography using a solution of 1.5% (10%  $\text{NH}_4\text{OH}$  in MeOH) in  $\text{CH}_2\text{Cl}_2$ . The product was obtained as a white amorphous solid, M.S. (Mass Spec)  $\text{M}^+ = 433$ .

- By essentially the same procedures as set forth in Example 75 above but using the compounds set forth in Column 1, Table 4 below, in place of 4-pyridylacetic acid, one can obtain compounds of the formula



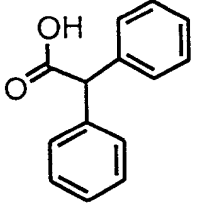
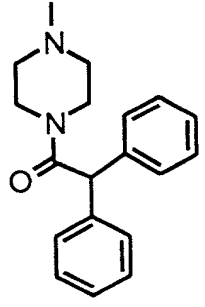
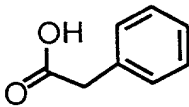
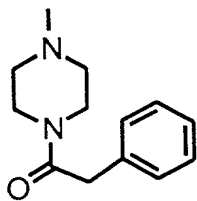
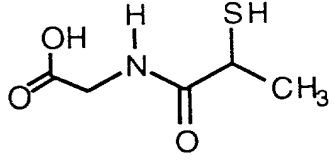
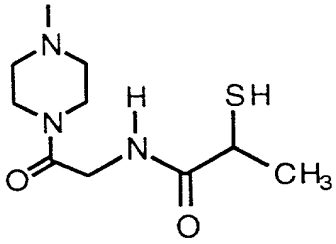
wherein R is as listed in Column 2 of Table 4.

15

TABLE 4

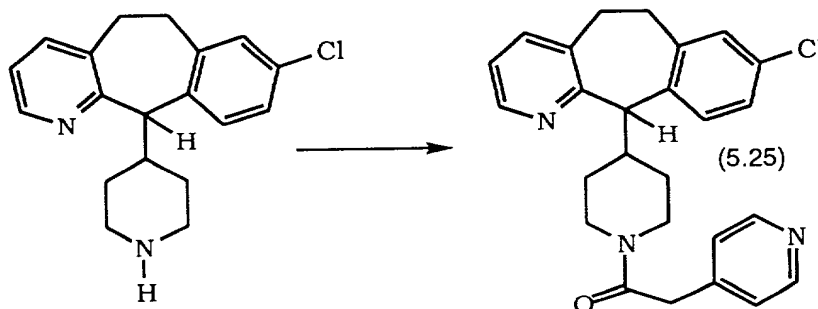
| EX. | COLUMN 1 | COLUMN 2 | CMPD   |
|-----|----------|----------|--|
| 76  |          |          | white<br>amorphous<br>solid<br>Mass Spec<br>$\text{M}^+ = 501$ |
| 77  |          |          | white<br>amorphous<br>solid<br>Mass Spec<br>$\text{M}^+ = 512$ |
| 78  |          |          | white<br>amorphous<br>solid<br>Mass Spec<br>$\text{M}^+ = 433$ |

TABLE 4 - continued

| EX. | COLUMN 1   | COLUMN 2  | CMPD   |
|-----|--|---|--|
| 79  |   |   | white<br>amorphous<br>solid<br>Mass Spec<br>M+ = 508 |
| 80  |   |   | white<br>amorphous<br>solid<br>Mass Spec<br>M+ = 432 |
| 81  |  |  | white<br>amorphous<br>solid<br>Mass Spec<br>M+ = 459 |

EXAMPLE 82

5 8-CHLORO-11-[1-(2-(4-PYRIDYL)ACETYL)-4-PIPERIDYL]-6,11-DIHYDRO-5H-BENZO[5,6]CYCLOHEPTA[1,2-b]-PYRIDINE

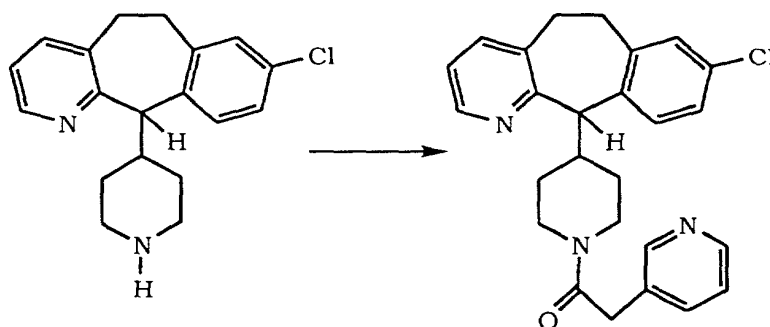


Dissolve 0.1 g (0.32 m mole) of 8-chloro-11-(4-piperidyl)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine (from Example 233),  
 10 0.06 g (0.32 m mole) of 4-pyridylacetic acid, 0.092 g (0.48 m mole) of DEC, 0.065 g (0.48 m mole) of HOBT and 0.048 g (0.50 m mole) of N-

methyl morpholine in 5 mL of DMF and stir at room temperature for 18 hours under nitrogen. Concentrate under vacuo and partition between 100 mL each of EtOAc and water. Dry the organic layer over sodium sulfate and concentrate under vacuo. The resulting residue is chromatographed on silica gel using 98% dichloro methane and 2% MeOH, saturated with ammonia as the solvent, giving the product as a white waxy solid, mass spec  $M^+ = 431$ .

#### EXAMPLE 82A

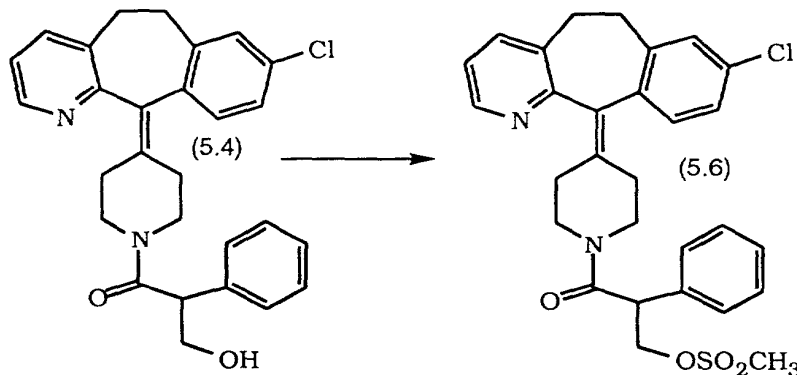
10 8-CHLORO-11-[1-(2-(PYRIDYL)ACETYL)-4-PIPERIDYL]-6,11-DIHYDRO-5H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDINE



By essentially the same procedure as set forth in Example 82, but using 3-pyridylacetic acid instead of 4-pyridylacetic acid, the title compound is obtained as a white solid ( $M^+ = 431$ , mp = 81.7-82°C).

#### EXAMPLE 83

20 8-CHLORO-11-[1-(2-METHYLSULFONYLOXY-1-PHENYLETHYL-CARBONYL)-4-PIPERIDYLIDENE]-6,11-DIHYDRO-5H-BENZO[5,6]-CYCLOHEPTA[1,2-b]-PYRIDINE

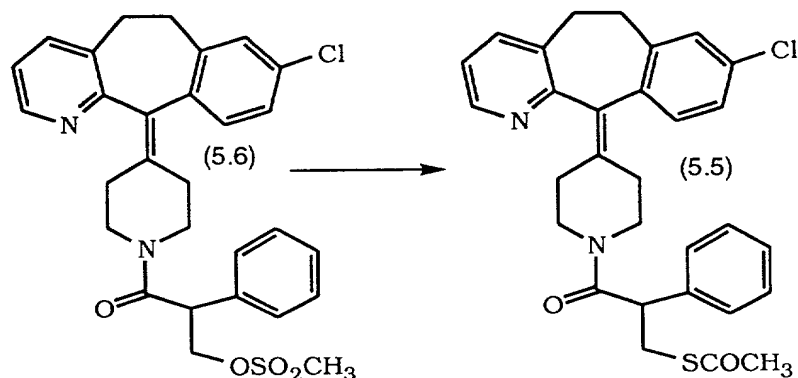


Dissolve 0.40 g (0.9 m mole) of 8-chloro-11-[1-(2-hydroxy-1-phenylethylcarbonyl)-4-piperidylidene]-6,11-dihydro-5H-benzo[5,6]-

cyclohepta-[1,2-b]pyridine (Example 41 of Table 2) in 10 mL of pyridine and stir under nitrogen. Add 0.15 g (1.3 m mole) of methanesulfonyl chloride and stir for 20 hours. Concentrate under vacuo and triturate the residue with ether. Purify the resulting solid by silica gel chromatography using 2% MeOH saturated with ammonia, and 98% CH<sub>2</sub>Cl<sub>2</sub> as the solvent. The product is obtained as a white solid, mp = 110.7-111.6° C.

#### EXAMPLE 84

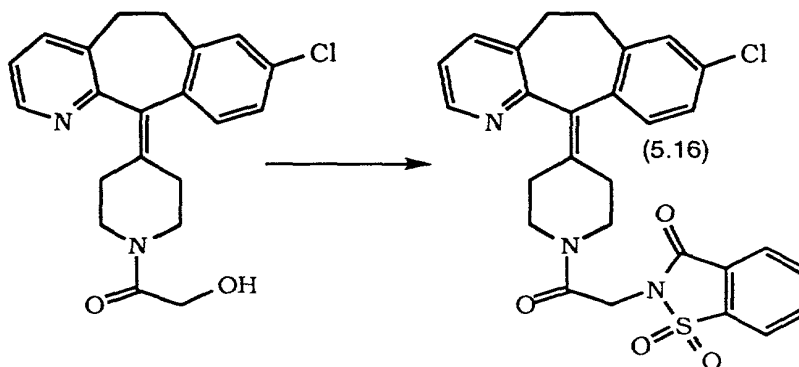
10 8-CHLORO-11-[1-(2-ACETYL MERCAPTO-1-PHENYLETHYL)-  
CARBONYL)-4-PIPERIDYLIDENE]-6,11-DIHYDRO-5H-BENZO[5.6]-  
CYCLOHEPTA[1.2-b]-PYRIDINE



Dissolve 0.3 g (0.56 m mole) of 8-chloro-11-[1-(2-methanesulfonyl-  
oxy-1-phenylethylcarbonyl)-4-piperidylidene]-6,11-dihydro-5H-benzo-  
15 [5,6]cyclohepta-[1,2-b]pyridine (Formula 5.6 of Example 83) in 5 mL of  
DMF and add 0.2 g (0.6 m mole) of cesium thioacetate (preparation  
described in Synthetic Communications, 13, 553, 1983). Stir the reaction  
at 80°C for twenty hours then concentrate under vacuo. Purify the residue  
by silica gel chromatography using 70% EtOAc and 30% hexane as the  
20 solvent. The product is obtained as a light brown solid, mp = 92.7-93°C.

EXAMPLE 85

8-CHLORO-11-[1-(1-(2,3-DIHYDRO-3-OXO-1,2-BENZOISOTHIAZOL-S,S-DIOXIDE-2-YL)METHYLCARBONYL)-4-PIPERIDYLIDENE]-6,11-DIHYDRO-5H-BENZO[5,6]CYCLOHEPTA[1,2-b]-PYRIDINE



5

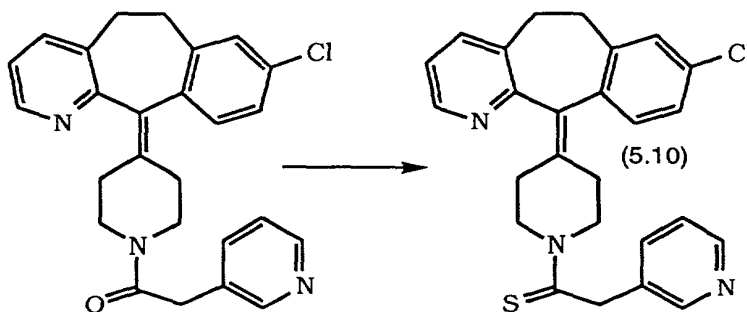
Dissolve 0.46g (1.7 m mole) of 8-chloro-11-[1-(2-hydroxyethyl-carbonyl)-4-piperidylidene]-6,11-dihydro-5H-benzo[5,6]cyclohepta-[1,2,b]pyridine (Example 49a of Table 2) in 30 mL of DMF and stir at 0°C under nitrogen. Add 0.55 g (2.1 m mole) of triphenyl phosphine and 0.36 g (2.1 m mole) of diethyl azodicarboxylate. Stir reaction mixture at 70°C for 3 days, then concentrate under vacuo. The residue was dissolved in 50 mL of 1 N HCl and washed with 100 mL of EtOAc. The water layer was neutralized with 1 N NaOH and the mixture was extracted with EtOAc. The organic layer was dried over MgSO<sub>4</sub> and concentrated under vacuo. The residue was purified by silica gel chromatography using 90% EtOAc and 10% hexane as the solvent, giving the product as a white solid, mass spec. M+ = 534.

10

15

EXAMPLE 86

8-CHLORO-11-[1-(1-(3-PYRIDYL)METHYLTHIOCARBONYL)-4-PIPERIDYLIDENE]-6,11-DIHYDRO-5H-BENZO[5,6]CYCLOHEPTA[1,2-b]-PYRIDINE

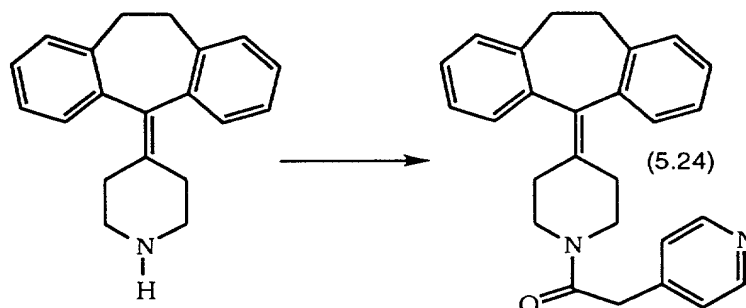


20

Dissolve 0.50 g (0.12 m mole) of 8-chloro-11-[1-(1-(3-pyridyl)-methylcarbonyl)-4-piperidylidene]-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine (Example 2 of Table 2) and 0.5 g (0.12 m mole) of 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (Lawesson's Reagent) in 15 mL of toluene and stir for 18 hours at room temperature and 18 hours at 80°C, under nitrogen. Filter the reaction mixture and concentrate under vacuo. Dissolve the residue in 50 mL of 1N HCl and extract with 200 mL of CH<sub>2</sub>Cl<sub>2</sub>. The water layer was neutralized with Na<sub>2</sub>CO<sub>3</sub> and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was dried over MgSO<sub>4</sub> and concentrated under vacuo giving the product as a white solid, mp = 92-93°C.

#### EXAMPLE 87

#### 10,11-DIHYDRO-5-[1-(1-(4-PYRIDYL)METHYLCARBONYL)-4-PIPERIDYLIDENE]-5H-DIBENZO[a,d]CYCLOHEPTENE

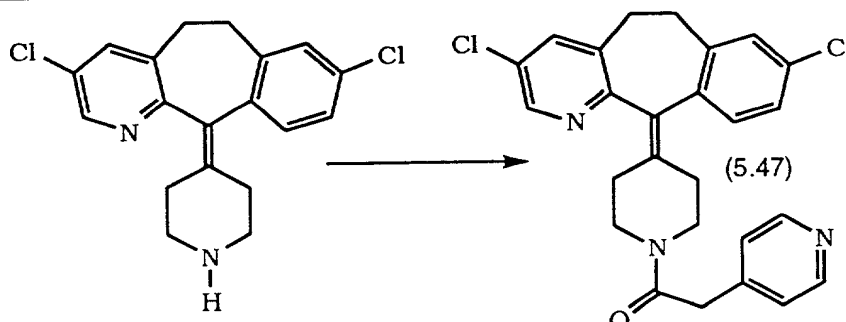


Dissolve 0.15 g (0.6m mole) of 10,11-dihydro-5-(4-piperidylidene)-5H-dibenzo[a,d]cycloheptene, 0.096 g (0.55 m mole) of 4-pyridylacetic acid hydrochloride, 0.16 g (0.83 m mole) of DEC and 0.075 g (0.55 m mole) of HOBT in 5 mL of DMF and stir at room temperature for 18 hours under nitrogen. Concentrate under vacuo and partition between 100 mL each of EtOAc and 10% aqueous sodium hydrogenphosphate. Dry the organic layer over MgSO<sub>4</sub> and concentrate under vacuo. The resulting residue is chromatographed on silica gel using 98% dichloro methane and 2% MeOH, saturated with ammonia as the solvent, giving the product as a white waxy solid, mp = 162.8-163.4 °C.



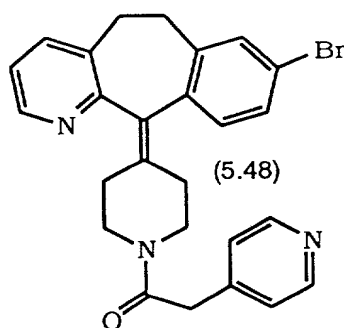
EXAMPLE 180

1-1-(4-PYRIDINYLACETYL)-4-[3,8-DICHLORO-5,6-DIHYDRO-11H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11-YLIDENE]-PIPERIDINE

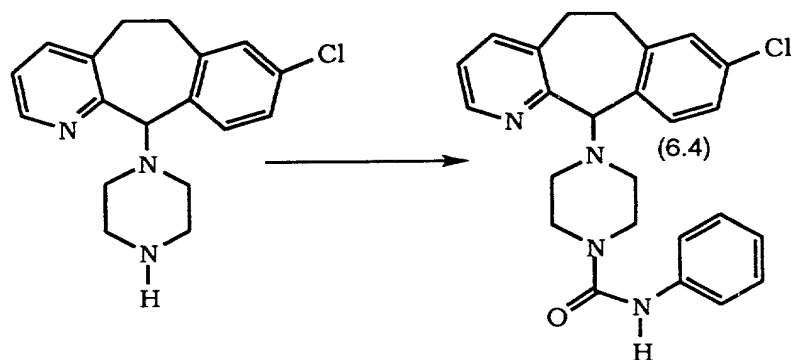


5 Dissolve 0.18 g (0.51 mmole) of 3,8-dichloro 11-(1-acetyl-4-piperidylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine, 0.088g (0.51 mmole) 4-pyridylacetic acid, 0.117g (0.61 mmole) of DEC, 0.082g (0.61 mmole) HOBT and 0.071g (0.71 mmole) N-methyl  
10 morpholine in 5 mL of DMF and stir for 18 hours under nitrogen. Concentrate under vacuo and partition between EtOAc and water. Dry organic layer over sodium sulfate and concentrate in vacuo. The resulting residue is chromatographed on silica gel using 95% CH<sub>2</sub>Cl<sub>2</sub> and 5% MeOH, saturated with ammonia as the solvent. The product is obtained as  
15 white solid, mp = 113-114 °C.

EXAMPLE 181

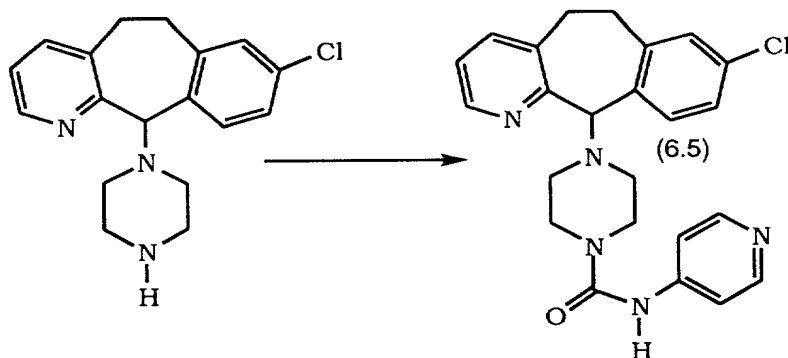


20 By essentially the same procedure as set forth in Example 180, but using 8-bromo-11-(1-acetyl-4-piperidylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine instead of 3,8-dichloro-11-(1-acetyl-4-piperidylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine, compound 5.48 was obtained as an off-white solid, mp= 94.3-94.7 °C.



To a stirred solution of phenyl isocyanate (1.27 mmole) in 15 ml of anhydrous  $\text{CH}_2\text{Cl}_2$  at room temperature and under an argon atmosphere was added dropwise over 20 minutes, a solution of 8-chloro-11-(1-piperazinyl)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine (1.27 mmole) in 5 ml of anhydrous  $\text{CH}_2\text{Cl}_2$ . The mixture was stirred at room temperature for 20 hours. The mixture was poured into 700 ml of  $\text{CH}_2\text{Cl}_2$  and washed with 100 ml of saturated  $\text{NaHCO}_3$ . The organic portion was dried over  $\text{MgSO}_4$ , filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography using a solution of 1.0% (10%  $\text{NH}_4\text{OH}$  in  $\text{MeOH}$ ) in  $\text{CH}_2\text{Cl}_2$ . The product was obtained as a white amorphous solid, M.S. (Mass Spec)  $M^+ = 433$ .

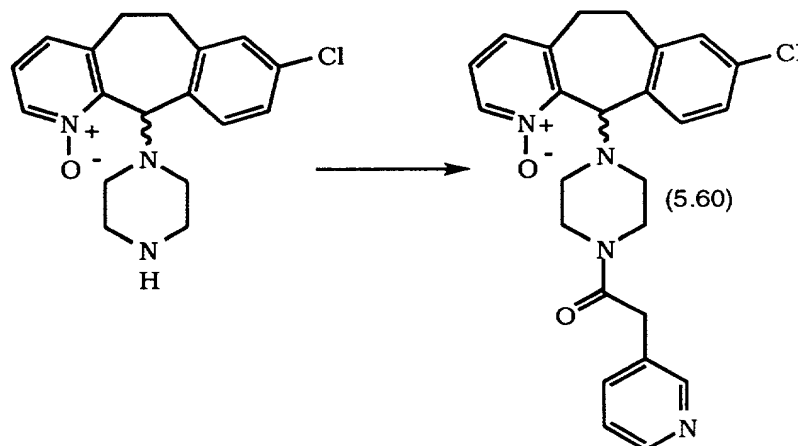
#### EXAMPLE 183



To a 5.0 ml reaction vial was added 8-chloro-11-(1-piperazinyl)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine (1.0 mmole) and N-ethoxycarbonyl-4-aminopyridine (0.99 mmole). The vial was capped and placed in an oil bath at  $170^\circ\text{C}$  and stirred for 5 hours. The residue was purified by silica gel chromatography using a solution of 3.0% (10%  $\text{NH}_4\text{OH}$  in  $\text{MeOH}$ ) in  $\text{CH}_2\text{Cl}_2$ . The product was obtained as a white amorphous solid, M.S. (Mass Spec)  $M^+ = 434$ .

EXAMPLE 184

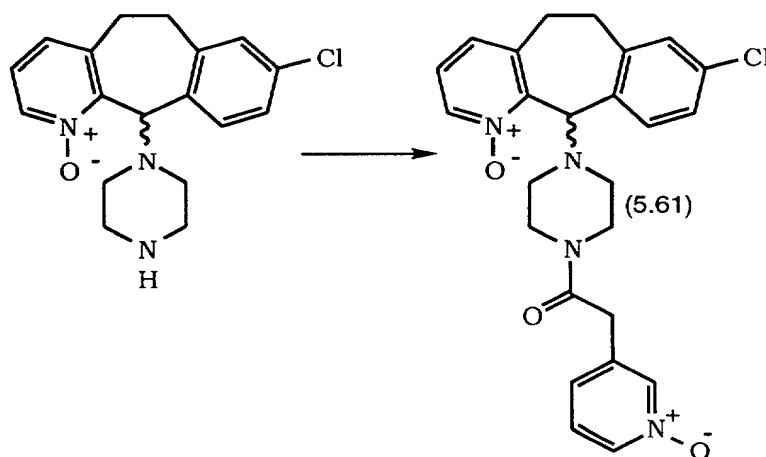
1-(8-CHLORO-6,11-DIHYDRO-5H-BENZO[5,6]CYCLOHEPTA  
[1,2-b]PYRIDIN-11-YL)-4-(3-PYRIDINYLAACETYL)piperazine 1-N-OXIDE



5        The title compound from Preparative Example 11D (0.5 grams) (1.5 mmoles) was reacted with 3-pyridylacetic acid (0.208 grams) (1.5 mmoles) under the conditions described in Example 75 to give the title compound (Yield: 0.439 grams, 95%,  $MH^+$  449).

EXAMPLE 185

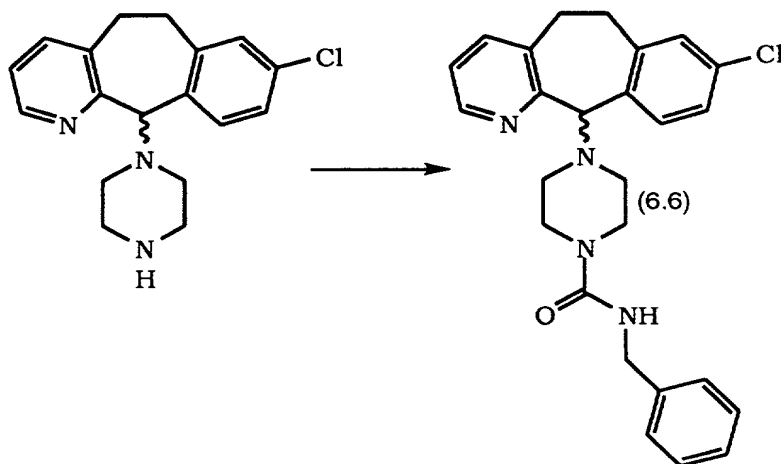
1-(8-CHLORO-6,11-DIHYDRO-5H-BENZO[5,6]CYCLOHEPTA  
[1,2-b]PYRIDIN-11-YL)-4-(3-PYRIDINYLAACETYL 1-N-OXIDE)PIPERAZINE  
1-N-OXIDE



15        The title compound from Preparative Example 11D (0.5 grams) (1.5 mmoles) was reacted with the title compound from Preparative Example 8 (0.232 grams) (1.5 mmoles) under the conditions described in Example 75 to give the title compound (Yield: 0.6454 grams, 92%,  $MH^+$  465.2).

EXAMPLE 186

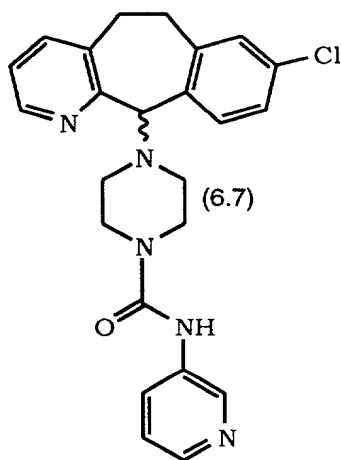
N-BENZYL 4-(8-CHLORO-6,11-DIHYDRO-5H-BENZO[5,6]CYCLO-  
HEPTA[1,2-b]PYRIDIN-11-YL)-1-PIPERAZINECARBOXAMIDE



The title compound from Example 75 was reacted with benzyl isocyanate under the conditions described in Example 182 above to give the title compound (Yield: 79%,  $MH^+$  447).

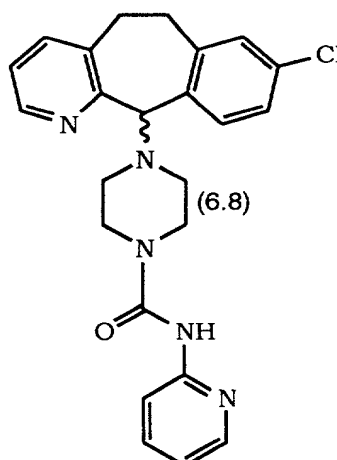
EXAMPLE 187

By essentially the same procedure as Example 183, with the exception that 3-ethoxycarbonylamino-pyridine or 2-ethoxycarbonylamino-pyridine (Preparative Example 12) is used instead of using 4-ethoxycarbonylamino-pyridine, the compound



White amorphous solid,  $MH^+$  434.3

or

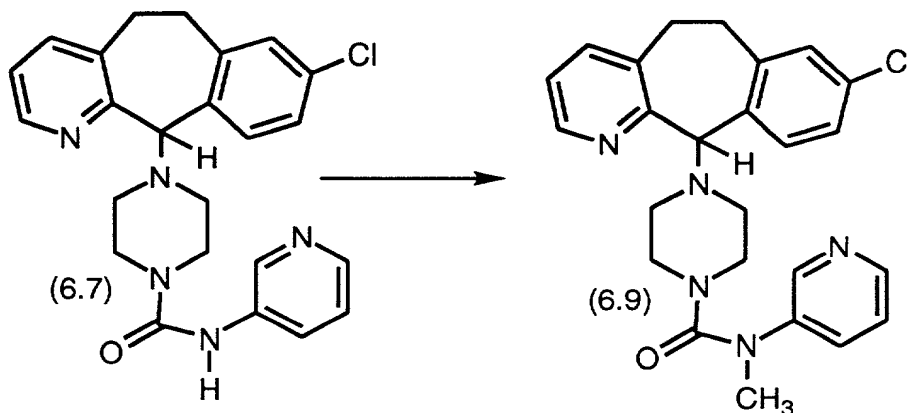


White amorphous solid,  $MH^+$  434.3

was obtained, respectively.

EXAMPLE 188

4-(8-CHLORO-6,11-DIHYDRO-5H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11-YL)-N-METHYL-N-(3-PYRIDINYL)-1-PIPERAZINE-CARBOXAMIDE



5

Compound 6.7 from Example 187 (10 grams) (23.1 mmoles) in DMSO (37.6 ml.) was added to a solution of powdered KOH (2.62 grams) (23.1 mmoles) in DMSO (25 ml.) and the mixture was stirred at 25°C for 3 minutes. Iodomethane (1.4518 ml.) (23.1 mmoles) was added and the mixture was stirred at 25°C for 15 minutes. The mixture was poured into water and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The latter was dried (magnesium sulphate), filtered and evaporated to dryness. The product was purified by chromatography on silica gel using 3-5%(10% concentrated ammonium hydroxide in MeOH)-CH<sub>2</sub>Cl<sub>2</sub> as the eluant to give the title compound (Yield: 6.28 grams, 61%, MH<sup>+</sup> 448).

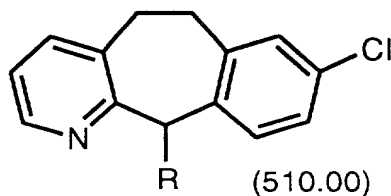
10

15

EXAMPLES 189 - 218

By essentially the same procedures as set forth in Example 75 above but using the compounds set forth in Column 1, Table 5 below, in place of 4-pyridylacetic acid, one can obtain compounds of the formula

20



wherein R is as listed in Column 2 of Table 5.

TABLE 5

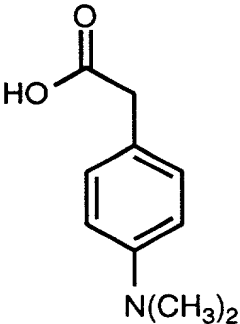
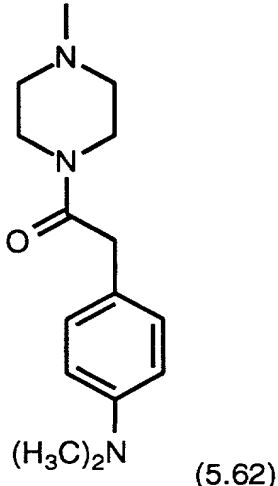
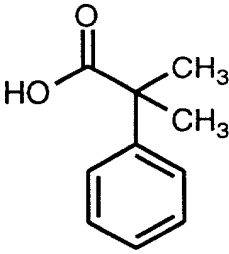
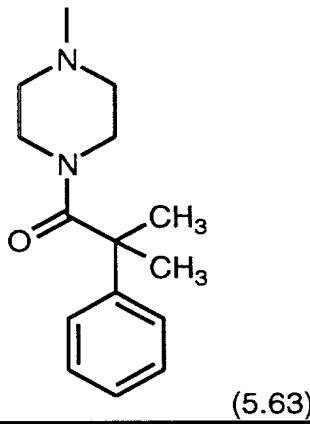
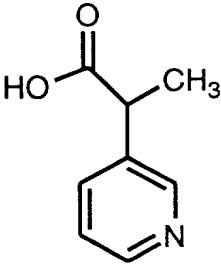
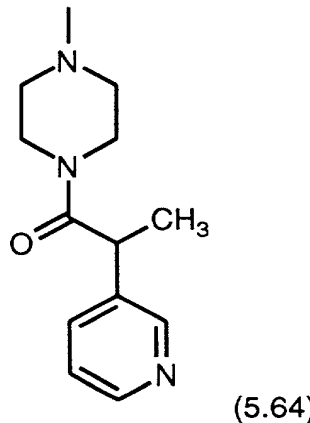
| EX. | COLUMN 1  | COLUMN 2   | CMPD   |
|-----|---|--|--|
| 189 |    | <br>(5.62)   | white<br>amorphous<br>solid<br>MH <sup>+</sup> 475 |
| 190 |   | <br>(5.63)  | white<br>amorphous<br>solid<br>MH <sup>+</sup> 460 |
| 191 |  | <br>(5.64) | white<br>amorphous<br>solid<br>MH <sup>+</sup> 447 |

TABLE 5 - continued

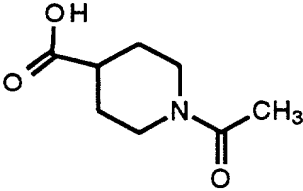
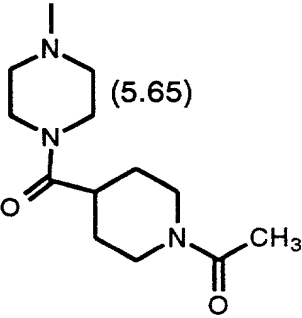
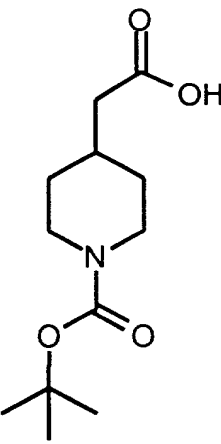
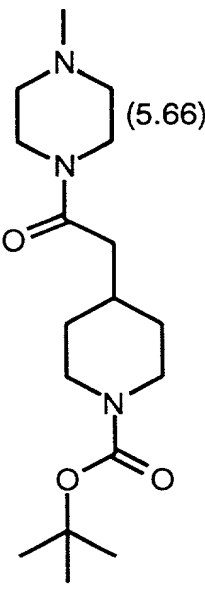
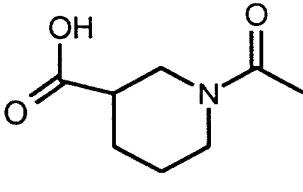
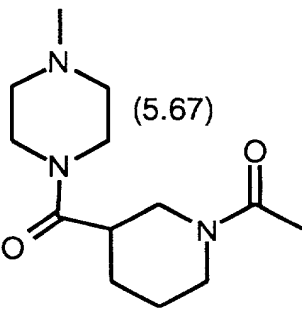
| EX. | COLUMN 1  | COLUMN 2   | CMPD   |
|-----|---|--|--|
| 192 |    |    | white<br>amorphous<br>solid<br>MH <sup>+</sup> 467 |
| 193 |   |   | white<br>amorphous<br>solid<br>MH <sup>+</sup> 539 |
| 194 |  |  | white<br>amorphous<br>solid<br>MH <sup>+</sup> 467 |

TABLE 5 - continued

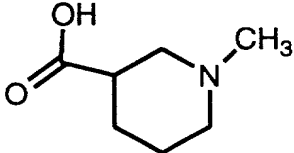
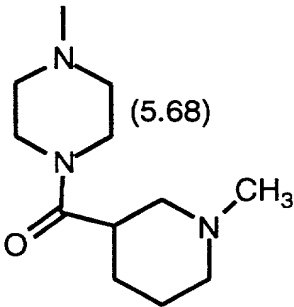
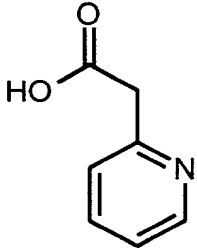
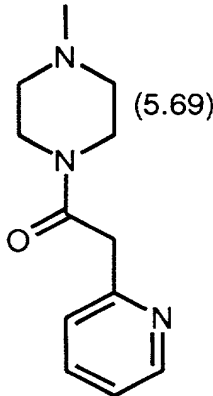
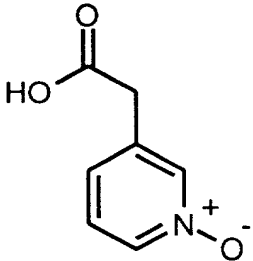
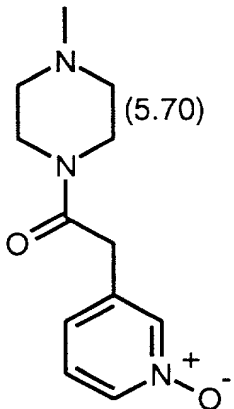
| EX. | COLUMN 1  | COLUMN 2   | CMPD   |
|-----|---|--|--|
| 195 |    |    | white<br>amorphous<br>solid<br>MH <sup>+</sup> 439 |
| 196 |    |   | white<br>amorphous<br>solid<br>MH <sup>+</sup> 433 |
| 197 |  |  | white<br>amorphous<br>solid<br>MH <sup>+</sup> 449 |



TABLE 5 - continued

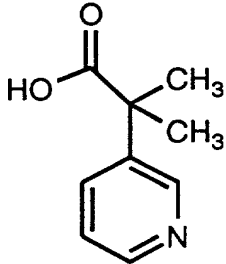
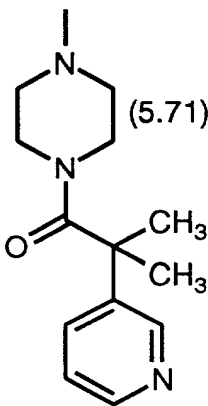
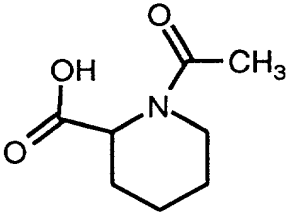
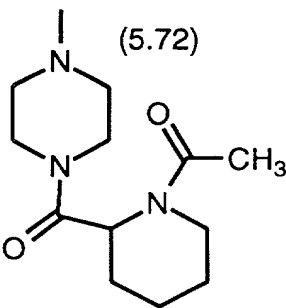
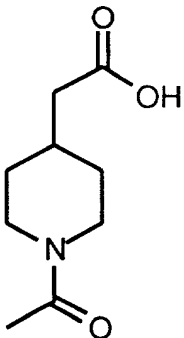
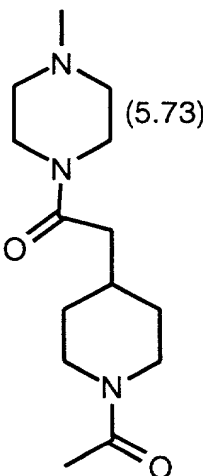
| EX. | COLUMN 1  | COLUMN 2  | CMPD   |
|-----|---|---|--|
| 198 |    |   | white<br>amorphous<br>solid<br>MH <sup>+</sup> 461 |
| 199 |   | <br><br>5.72A = Isomer A<br>5.72B = Isomer B | white<br>amorphous<br>solid<br>MH <sup>+</sup> 467 |
| 200 |  |   | white<br>amorphous<br>solid<br>MH <sup>+</sup> 467 |

TABLE 5 - continued

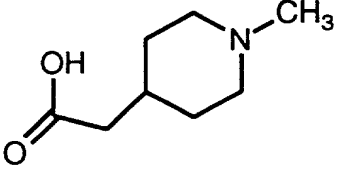
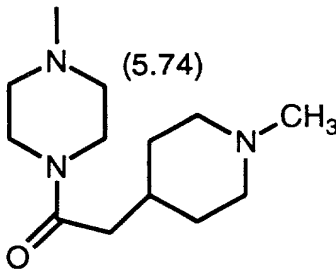
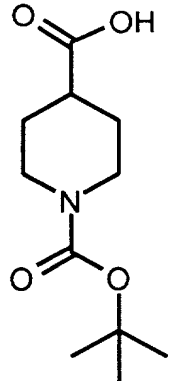
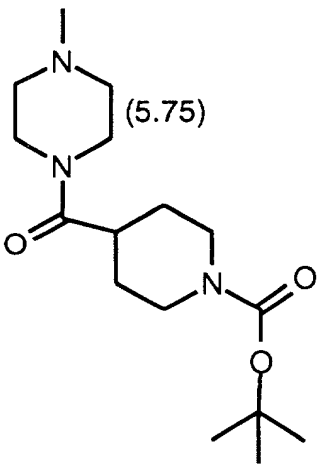
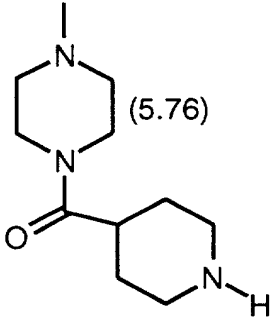
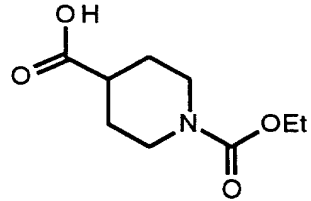
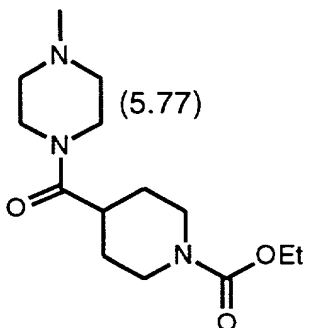
| EX. | COLUMN 1  | COLUMN 2   | CMPD   |
|-----|---|--|--|
| 201 |    |    | white<br>amorphous<br>solid<br>MH <sup>+</sup> 453 |
| 202 |   |   | white<br>amorphous<br>solid<br>MH <sup>+</sup> 525 |
| 203 | Trifluoroacetic Acid<br>deprotection of<br>Compound 5.75<br>of Example 202          |  | white<br>amorphous<br>solid<br>MH <sup>+</sup> 525 |
| 204 |  |  | white<br>amorphous<br>solid<br>MH <sup>+</sup> 497 |

TABLE 5 - continued

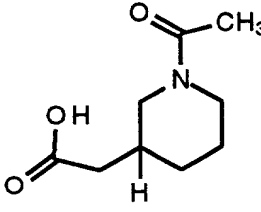
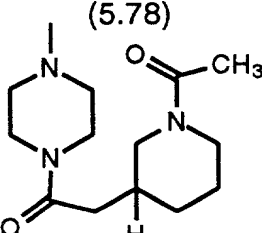
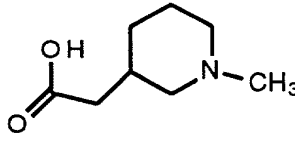
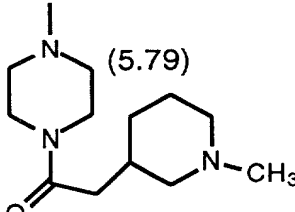
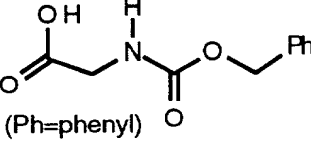
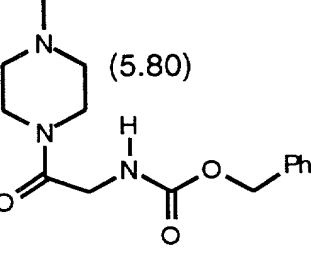
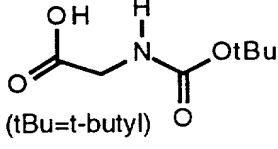
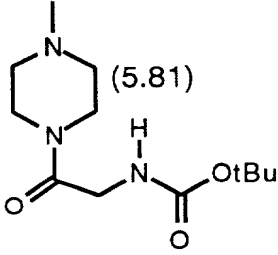
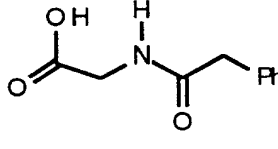
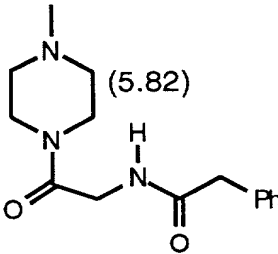
| EX. | COLUMN 1   | COLUMN 2   | CMPD   |
|-----|--|--|--|
| 205 |                     | (5.78)<br>   | white<br>amorphous<br>solid<br>MH <sup>+</sup> 481 |
| 206 |                     | (5.79)<br>   | white<br>amorphous<br>solid<br>MH <sup>+</sup> 453 |
| 207 | <br>(Ph=phenyl)    | (5.80)<br>  | white<br>amorphous<br>solid<br>MH <sup>+</sup> 505 |
| 208 | <br>(tBu=t-butyl) | (5.81)<br> | white<br>amorphous<br>solid<br>MH <sup>+</sup> 471 |
| 209 |                   | (5.82)<br> | white<br>amorphous<br>solid<br>MH <sup>+</sup> 489 |

TABLE 5 - continued

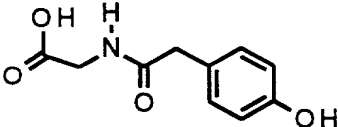
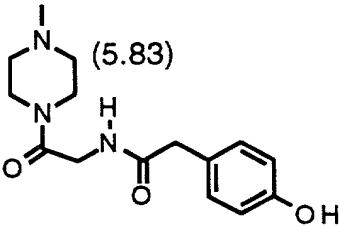
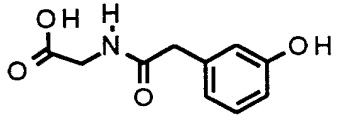
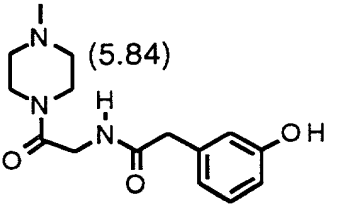
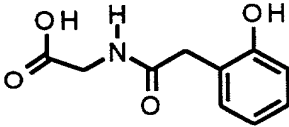
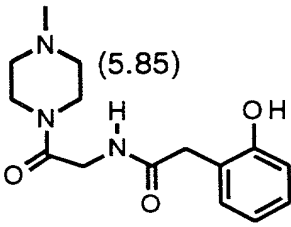
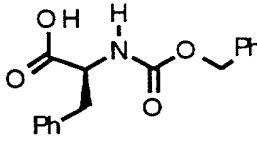
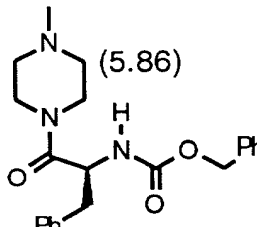
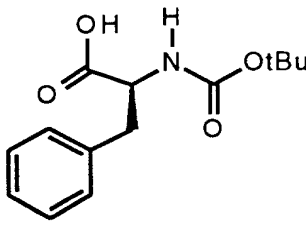
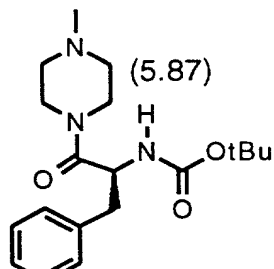
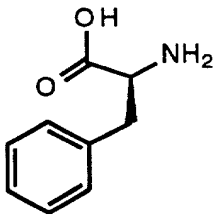
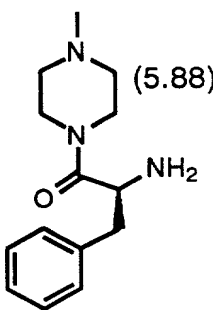
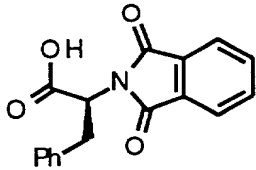
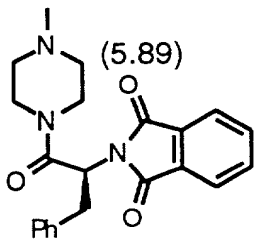
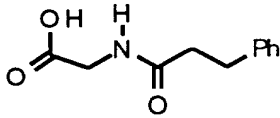
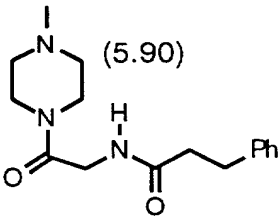
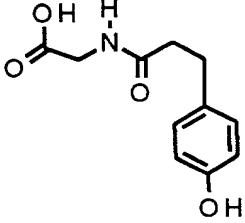
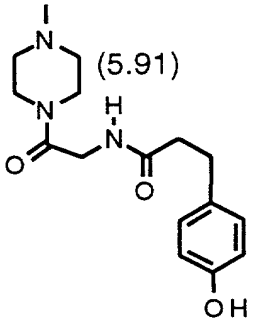
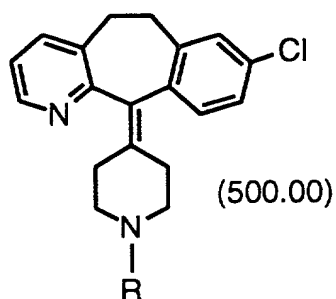
| EX. | COLUMN 1  | COLUMN 2   | CMPD   |
|-----|---|--|--|
| 210 |    |    | white<br>amorphous<br>solid<br>MH <sup>+</sup> 505 |
| 211 |    |    | white<br>amorphous<br>solid<br>MH <sup>+</sup> 505 |
| 212 |   |   | white<br>amorphous<br>solid<br>MH <sup>+</sup> 505 |
| 213 |  |  | white<br>amorphous<br>solid<br>MH <sup>+</sup> 595 |
| 214 |  |  | white<br>amorphous<br>solid<br>MH <sup>+</sup> 561 |

TABLE 5 - continued

| EX. | COLUMN 1  | COLUMN 2   | CMPD   |
|-----|---|--|--|
| 215 |    |    | white<br>amorphous<br>solid<br>MH <sup>+</sup> 461 |
| 216 |    |    | white<br>amorphous<br>solid<br>MH <sup>+</sup> 591 |
| 217 |   |   | white<br>amorphous<br>solid<br>MH <sup>+</sup> 503 |
| 218 |  |  | white<br>amorphous<br>solid<br>MH <sup>+</sup> 519 |

EXAMPLE 219 - 222

- 5 By essentially the same procedure as set forth in Example 1, but using the acids set forth in Column 1 of Table 6 below in place of 4-pyridylacetic acid, the compounds listed in Column 2 of Table 6 are obtained. The compounds listed in Table 6 refer to compounds of Formula 500.00:



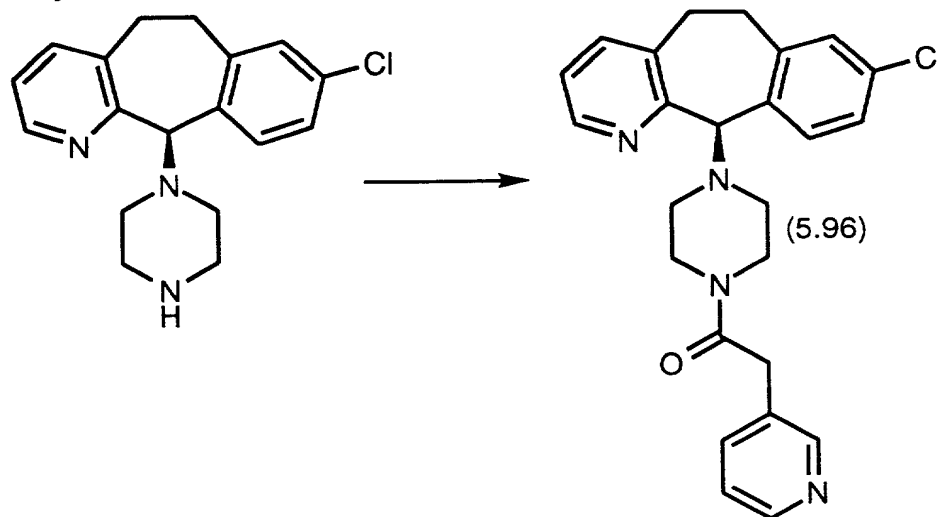
wherein R is the substituent in Column 2.

TABLE 6

| EX. | COLUMN 1 | COLUMN 2 | CMPD  |
|-----|----------|----------|---|
| 219 |          | (5.92)   | white<br>amorphous<br>solid<br>MH <sup>+</sup> 482<br>m.p. =<br>192-193°C |
| 220 |          | (5.93)   | white<br>amorphous<br>solid<br>MH <sup>+</sup> 502<br>m.p. =<br>282-285°C |
| 221 |          | (5.94)   | white<br>amorphous<br>solid<br>MH <sup>+</sup> 485                        |
| 222 |          | (5.95)   | white<br>amorphous<br>solid<br>MH <sup>+</sup> 514                        |

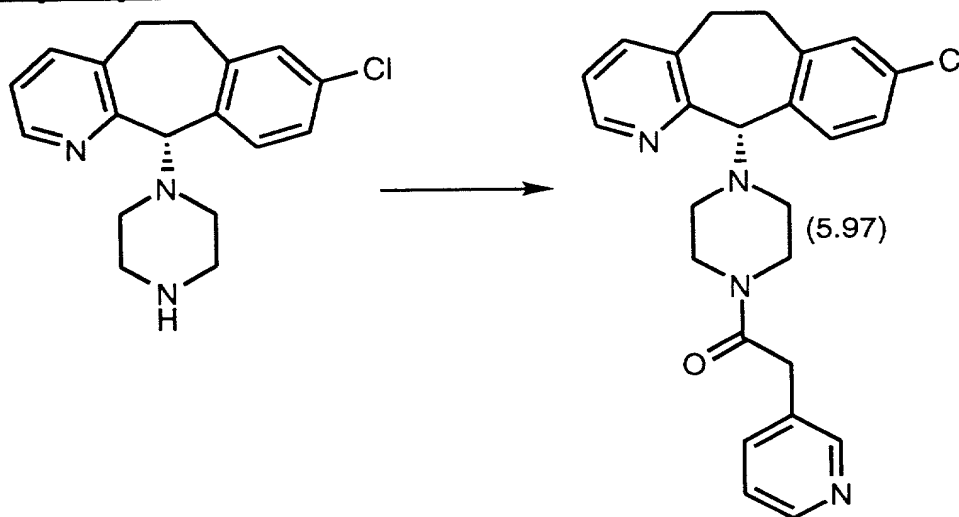
EXAMPLE 223

A. (+)-1-(8-CHLORO-5,6-DIHYDRO-11H-BENZO[5,6]CYCLO-  
HEPTA[1,2-b]PYRIDIN-11(R)-YL)-4-(3-PYRIDINYLA-  
CETYL)PIPERAZINE



- 5        The title R(+) diastereoisomer from Preparative Example 19 was reacted with 3-pyridylacetic acid under the same conditions as described in Example 75 to give the title compound (Yield: 88%, MH<sup>+</sup> 433).

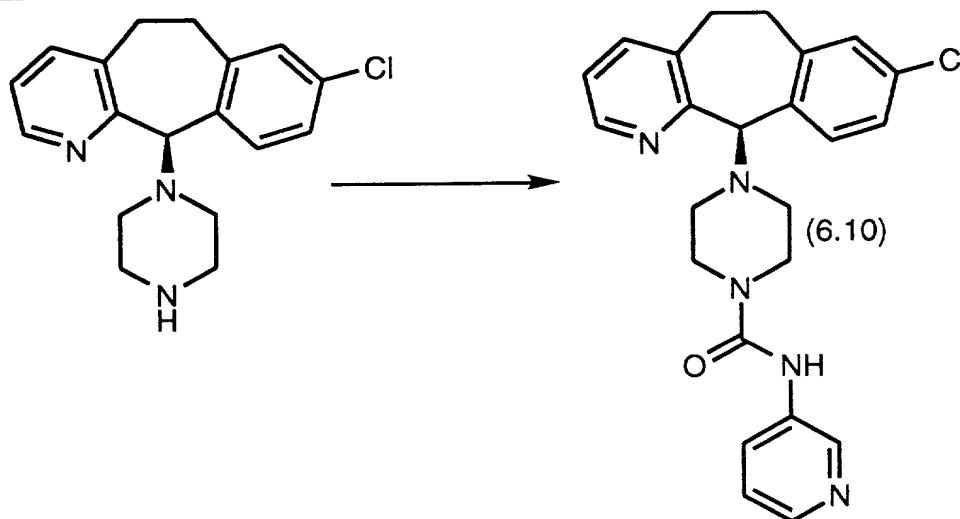
B. (-)-1-(8-CHLORO-5,6-DIHYDRO-11H-BENZO[5,6]CYCLO-  
HEPTA[1,2-b]PYRIDIN-11(S)-YL)-4-(3-PYRIDINYLA-  
CETYL)PIPERAZINE



- 10        The title S(-) diastereoisomer from Preparative Example 19 above was reacted with 3-pyridylacetic acid under the same conditions as described in Example 75 to give the title compound (Yield: 96%, MH<sup>+</sup> 433).

EXAMPLE 224

A. (+)-4-(8-CHLORO-6,11-DIHYDRO-5H-BENZO[5.6]CYCLO-  
HEPTA[1.2-b]PYRIDIN-11(R)-YL)-N-(3-PYRIDINYL)-1-PIPERAZINE-  
CARBOXYLATE

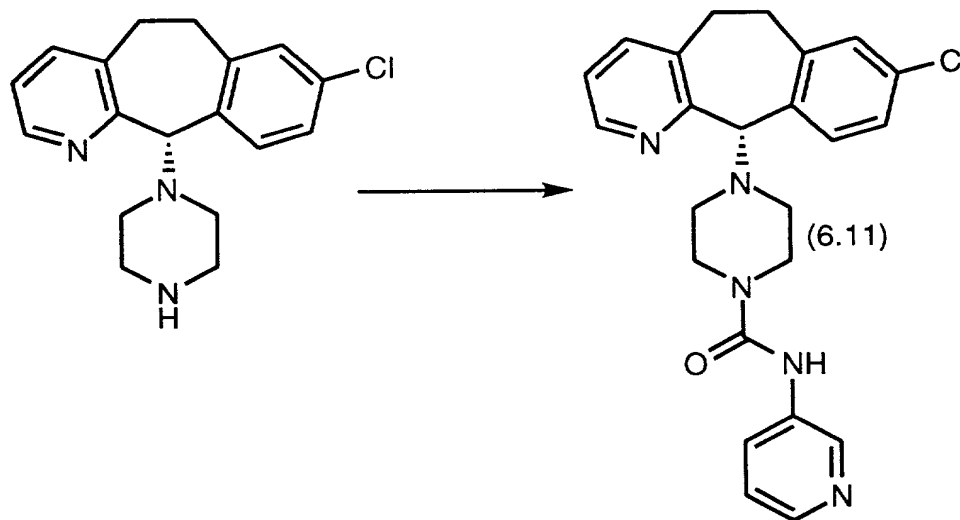


5

The title R(+) diastereoisomer from Preparative Example 19 was reacted with 3-ethoxycarbonylaminopyridine under the same conditions as described in Example 75 to give the title compound (Yield: 81%,  $MH^+$  434).

10

B. (-)-4-(8-CHLORO-6,11-DIHYDRO-5H-BENZO[5.6]CYCLO-  
HEPTA[1.2-b]PYRIDIN-11(S)-YL)-N-(3-PYRIDINYL)-1-PIPERAZINE-  
CARBOXAMIDE



The title S(-) diastereoisomer from Preparative Example 19 was reacted with 3-ethoxycarbonylaminopyridine under the same conditions

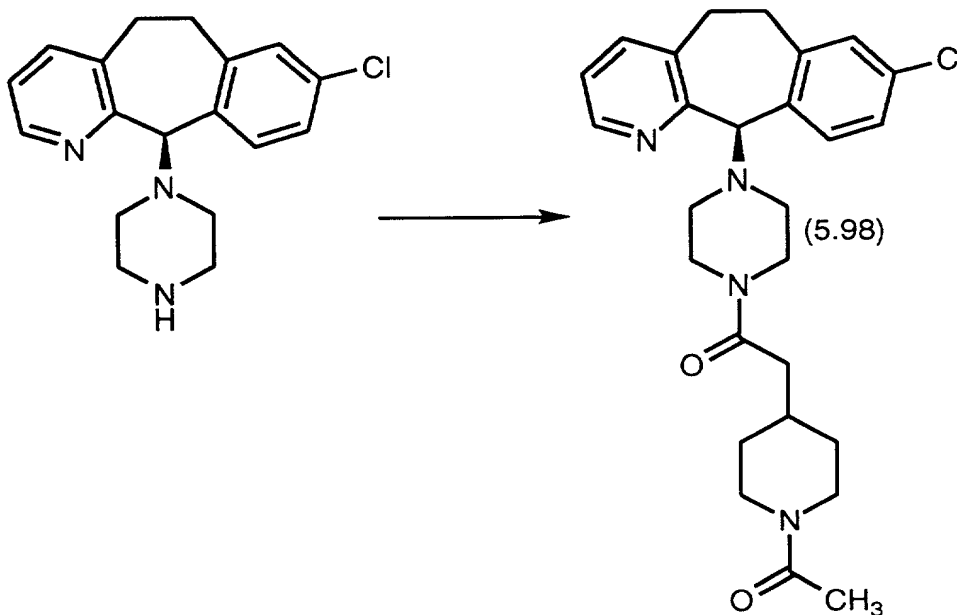
15



as described in Example 75 to give the title compound (Yield: 80%,  $MH^+$  434).

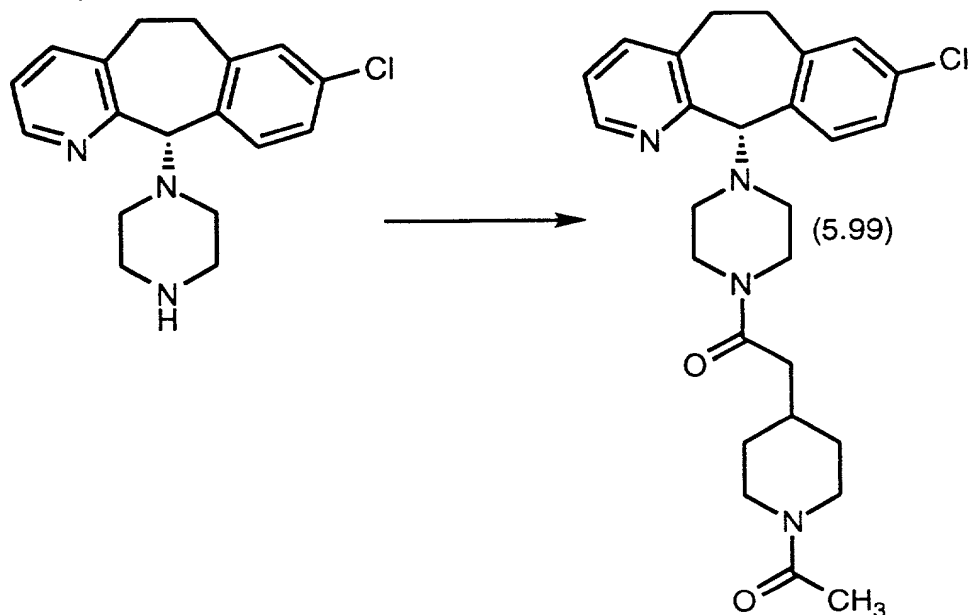
**EXAMPLE 225**

- 5      A.    (+)-1-(8-CHLORO-5,6-DIHYDRO-11H-BENZO[5,6]CYCLO-  
HEPTA[1,2-b]PYRIDIN-11(R)-YL)-4-[(1-ACETYL-4-PIPERIDINYL)-  
ACETYL]PIPERAZINE



- 10      The title R(+) diastereoisomer from Preparative Example 19 above was reacted with 1-N-acetylpiperidinyl-3-acetic acid under the same conditions as described in Example 75 to give the title compound (Yield: 52%,  $MH^+$  481).

B. (-)-1-(8-CHLORO-5,6-DIHYDRO-11H-BENZO[5,6]CYCLO-  
HEPTA[1,2-b]PYRIDIN-11(S)-YL)-4-[(1-ACETYL-4-PIPERIDINYL)-  
ACETYL]PIPERAZINE

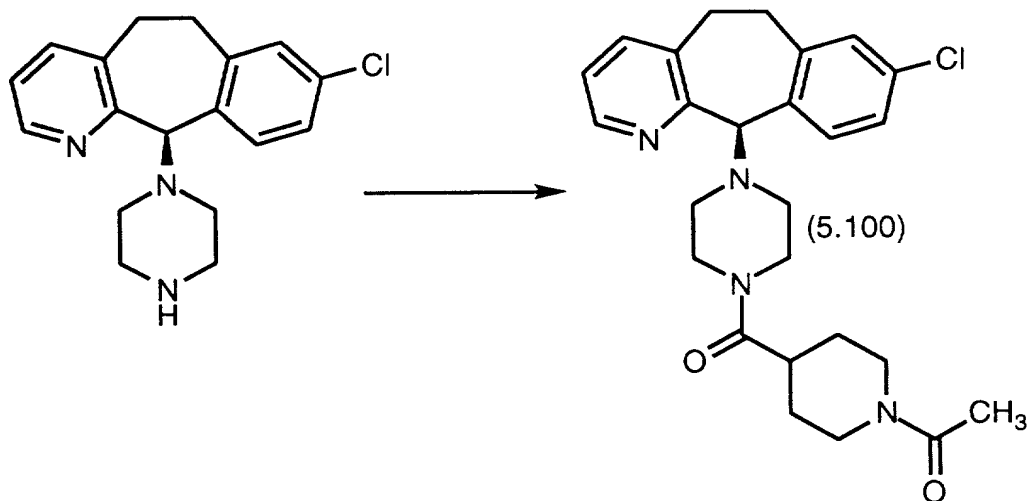


- 5 The title S(-) diastereoisomer from Preparative Example 19 above was reacted with 1-N-acetylpiperidinyl-3-acetic acid under the same conditions as described in Example 75 to give the title compound (Yield: 53%,  $MH^+$  481).

10

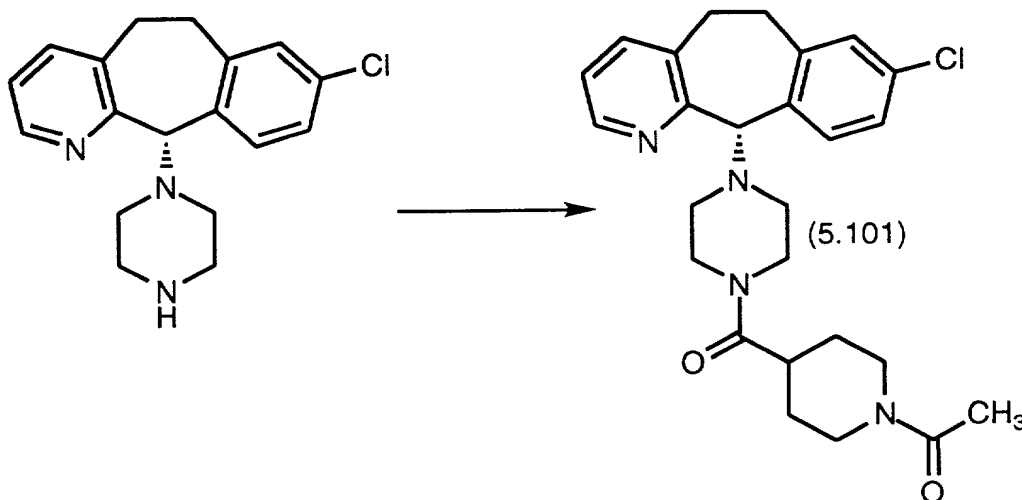
EXAMPLE 226

A. (+)-1-(8-CHLORO-6,11-DIHYDRO-5H-BENZO[5,6]CYCLO-  
HEPTA[1,2-b]PYRIDIN-11(R)-YL)-4-[(1-ACETYL-4-PIPERIDINYL)-  
CARBONYL]PIPERAZINE



The title R(+) diastereoisomer from Preparative Example 19 was reacted with 1-N-acetylisonipecotic acid under the same conditions as described in Example 75 to give the title compound (Yield: 90%, MH<sup>+</sup> 467).

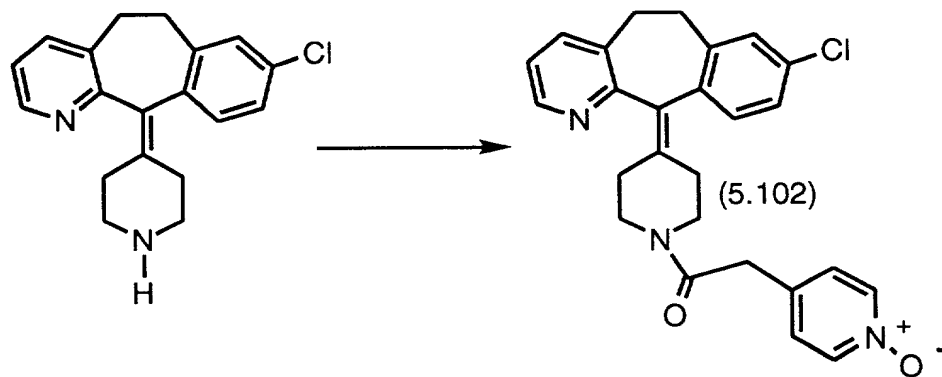
- 5        B.    (-)-1-(8-CHLORO-6,11-DIHYDRO-5H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11(S)-YL)-4-[(1-ACETYL-4-PIPERIDINYL)-CARBONYL]PIPERAZINE



- 10        The title S(-) diastereoisomer from Preparative Example 19 was reacted with 1-N-acetylisonipecotic acid under the same conditions as described in Example 75 to give the title compound (Yield: 93%, MH<sup>+</sup> 467).

#### EXAMPLE 227

- 15        4-(8-CHLORO-5,6-DIHYDRO-11H-BENZO-[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11-YLIDENE)-1-[(4-PYRIDINYL)ACETYL]- PIPERIDINE N1 OXIDE

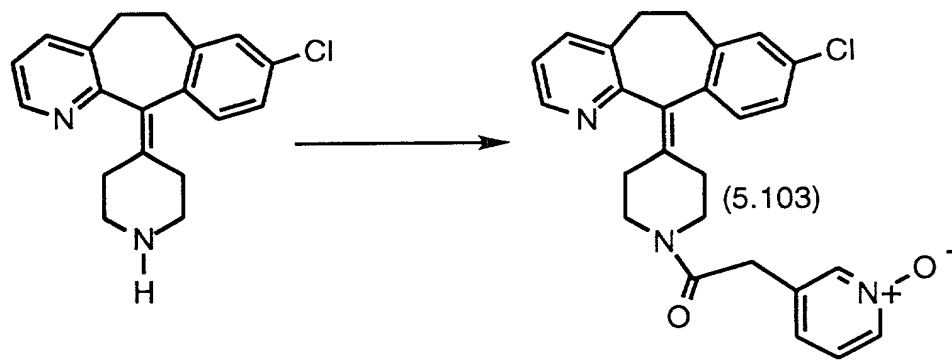


To a mixture of 0.933g(3 mmol) of 4-(8-chloro-5,6-dihydro-11H-benzo-[5,6]cyclohepta(1,2-b)pyridin-11-ylidene)-piperidine (product from Preparative Example 1, step G), 0.46g(3 mmol) of 4-pyridyl acetic acid N-oxide (prepared as described in Preparative Example 8) 1-hydroxybenzo-  
 5 triazole (0.40g, 3 mmol) in 20 mL of DMF at ~ 4°C and under nitrogen atmosphere was added N- methyl morpholine(1.65 mL, 15 mmol) followed by DEC an reaction stirred overnight at room temperature. The volatiles were stripped off and the resulting semi-solid was partitioned between water and EtOAc. The aqueous phase was washed twice with EtOAc.  
 10 Combined EtOAc fractions were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated. The crude product was purified via flash chromatography on silica gel (first eluting with 3% and then 5% MeOH saturated with ammonia in CH<sub>2</sub>Cl<sub>2</sub>) to give the title compound as a light brown solid(0.2g mp=128-130 °C MH<sup>+</sup>446).

15

#### EXAMPLE 228

4-(8-CHLORO-5,6-DIHYDRO-11H-BENZO-[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11-YLIDENE)-1-[(3-PYRIDINYL)ACETYL]-PIPERIDINE N1 OXIDE



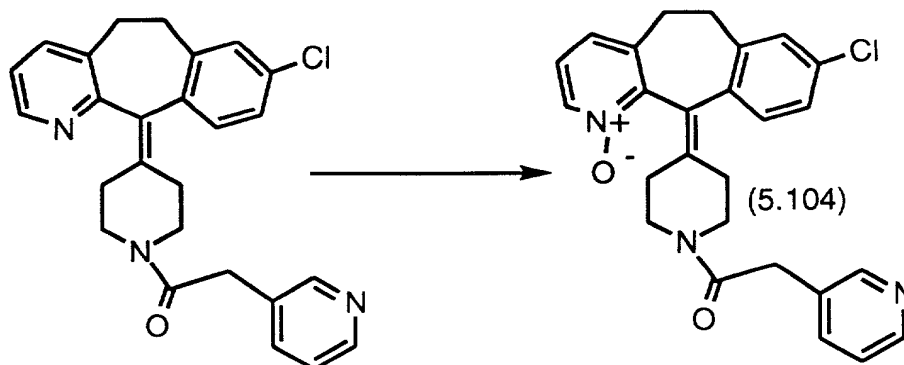
20

By essentially the same procedure as set forth in Example 227, but using 3-pyridyl acetic acid N-oxide (Preparative Example 9) instead of 4-pyridyl acetic acid N-oxide the title compound was obtained as a white solid (mp = 120-121°C, MH<sup>+</sup>=466).

25

EXAMPLE 229

4-(8-CHLORO-5,6-DIHYDRO-11H-BENZO-[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11-YLIDENE)-1-[(3-PYRIDINYL)ACETYL]- PIPERIDINE N4 OXIDE

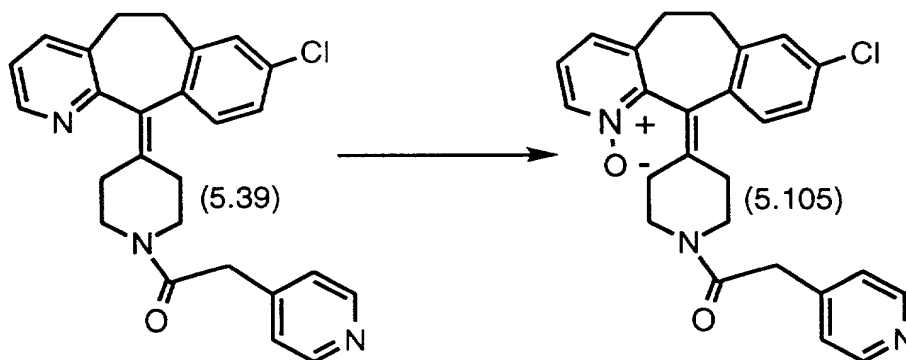


5  
4-(8-chloro-5,6-dihydro-11H-benzo-[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-1-[(3-pyridinyl)acetyl]-piperidine (1.0g, 2.33mmol) was dissolved in dry CH<sub>2</sub>Cl<sub>2</sub>(50mL) at -10°C. MCPBA (80-85% purity 1.1g, 5.13 mmol) was added and the reaction stirred at that temperature for 95  
10 minutes. The reaction mixture was washed with sodium bisulfite and then with 10% NaOH. The organic phase was dried over MgSO<sub>4</sub> and then concentrated. Purification on silica gel eluting, first with 4%, 6% and then 10% MeOH in CH<sub>2</sub>Cl<sub>2</sub> gave rise to the title compound as a white solid (0.2g, 0.77 mmol MH<sup>+</sup>=446).

15

EXAMPLE 230

4-(8-CHLORO-5,6-DIHYDRO-11H-BENZO-[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11-YLIDENE)-1-[(4-PYRIDINYL)ACETYL]- PIPERIDINE N4 OXIDE



20

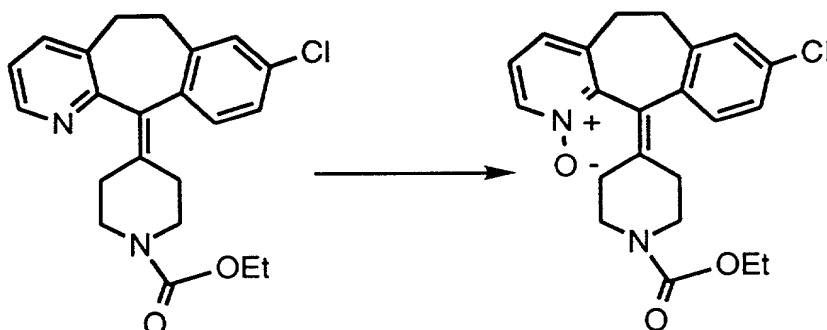
By essentially the same procedures as set forth in Example 229 above, but using 4-(8-chloro-5,6-dihydro-11H-benzo-[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-1-[(4-pyridinyl)acetyl]-piperidine instead of 4-(8-

chloro-5,6-dihydro-11H-benzo-[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-1-[(3-pyridinyl)acetyl]-piperidine the title compound was obtained as an off-white solid ( $MH^+=446$ ).

5

EXAMPLE 231

A. 8-CHLORO-11-(1-ETHOXYCARBONYL-4-PIPERIDYLIDENE)-6,11-DIHYDRO-5H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDINE N-OXIDE

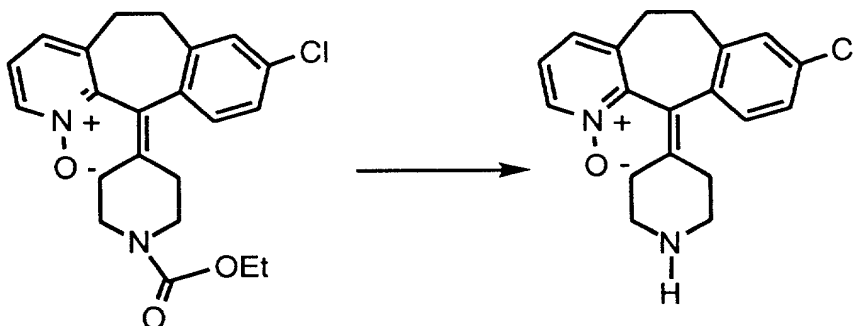


10

8-chloro-11-(1-ethoxycarbonyl-4-piperidylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine (5g, 13.06 mmol) was dissolved in  $CH_2Cl_2$  at  $-10^\circ C$ . 3-Chlorobenzoic acid (4.9g, 15.67 mmol) was then added and the reaction mixture stirred for 95 minutes. The reaction mixture was taken up in  $CH_2Cl_2$  and extracted with sodium bisulfite, 10% NaOH. The crude reaction product was purified on silica gel eluting first with 1% and then with 2% MeOH in  $CH_2Cl_2$  to give the title compound (2.7g,  $MH^+ 399$ ).

15

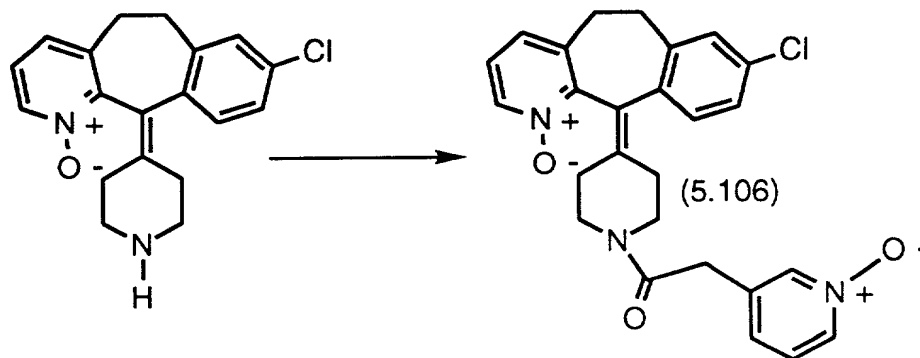
20 B. 8-CHLORO-11-(4-PIPERIDYLIDENE)-6,11-DIHYDRO-5H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDINE N-OXIDE



By essentially the same procedures as set forth in Preparative Example 1 step G, but using 8-chloro-11-(1-ethoxycarbonyl-4-piperidylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine N-

oxide instead of 8-chloro-11-(1-ethoxycarbonyl-4-piperidylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine, the title compound was obtained and used for the next reaction without further purification (MH+ 327).

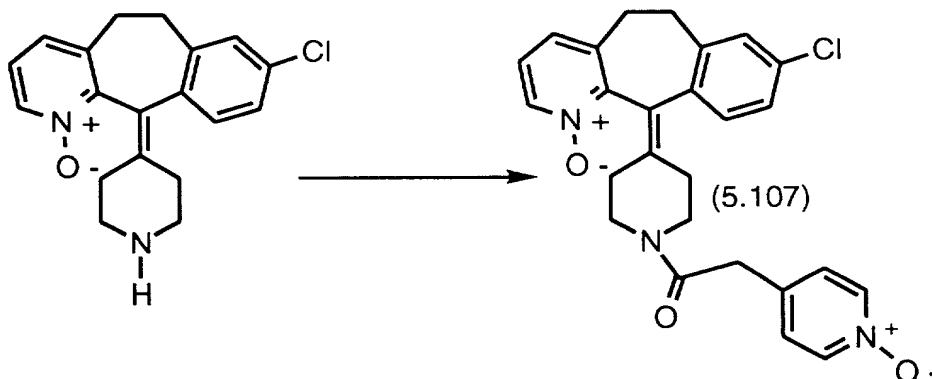
5 C. 4-(8-CHLORO-5,6-DIHYDRO-11H-BENZO[5,6]CYCLOHEPTA(1,2-b)PYRIDIN-11-YLIDENE)-1-[(3-PYRIDINYL)ACETYL]-PIPERIDINE N1,N4 DIOXIDE



By essentially the same procedure as set forth in Example 227, but  
 10 using 3-pyridyl acetic acid N-oxide (Preparative Example 9) instead of 4-pyridyl acetic acid N-oxide and 8-chloro-11-(4-piperidylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine N-oxide instead of 8-chloro-11-(4-piperidylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine, the title compound was obtained as a white solid (mp=105-  
 15 107°C, MH+=462).

EXAMPLE 232

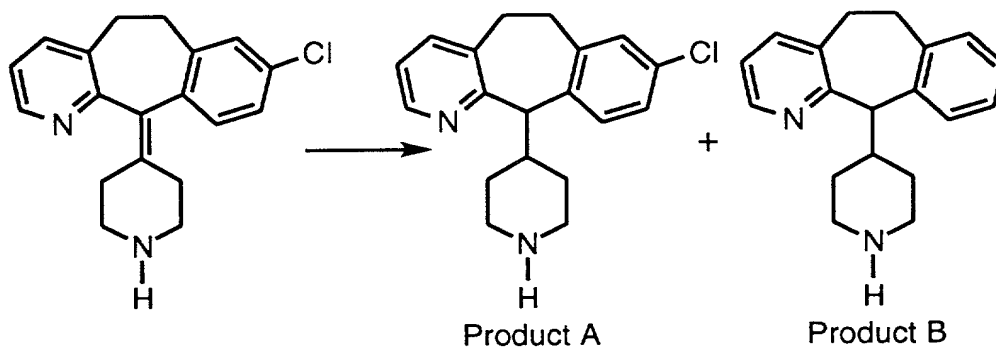
20 4-(8-CHLORO-5,6-DIHYDRO-11H-BENZO-[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11-YLIDENE)-1-[(4-PYRIDINYL)ACETYL]-PIPERIDINE N1,N4 DIOXIDE



By essentially the same procedure as set forth in Example 227, but using 8-chloro-11-(4-piperidylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine N-oxide instead of 8-chloro-11-(4-piperidylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine, the title compound was obtained as a light brown solid(  $MH^+=462$ ).

### EXAMPLE 233

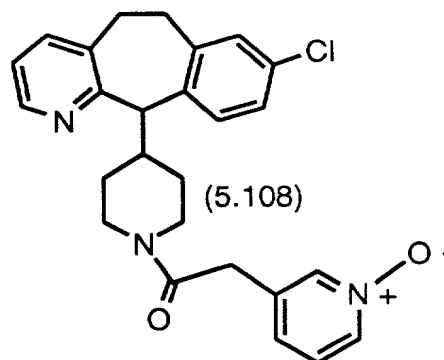
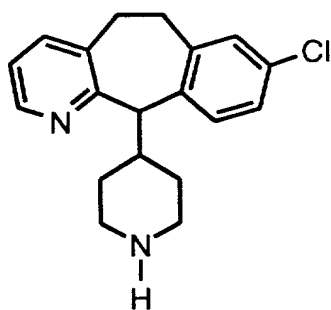
A. 8-CHLORO-6,11-DIHYDRO-11-(4-PIPERIDINYL)-5H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDINE (Product A) and  
6,11-DIHYDRO-11-(4-PIPERIDINYL)-5H-BENZO[5,6]-  
CYCLOHEPTA[1,2-b]PYRIDINE (Product B)



To a solution 66.27g (0.21mole) of 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta(1,2-b)pyridin-11-ylidene)-piperidine (product from Preparative Example 1 Example, step G), in THF (1L) was added lithium aluminum hydride (24.32g, 0.64 mole) and the reaction mixture was heated to reflux overnight. The reaction mixture was then cooled to room temperature and ~ 3L of diethyl ether is added followed by dropwise addition of saturated sodium sulfate until a white gray precipitate forms.  $MgSO_4$  was then added to the separated organic layer and stirred for 30 minutes. All the volatiles were then removed and the resulting crude mixture was chromatographed on a silica gel column eluting with 10% MeOH saturated with ammonia in  $CH_2Cl_2$ . The material obtained contained both the desired compound and the des-chloro compound. Separation on HPLC using reverse phase column and eluting with 40% MeOH-water afforded the desired compounds as white solids (Product A's mp = 95.2-96.1°C, Product B's mp = 145.1-145.7°C).

B. 4-(8-CHLORO-6,11-DIHYDRO-5H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11-YL)-1-[(3-PYRIDINYL)ACETYL]-PIPERIDINE  
N1 OXIDE



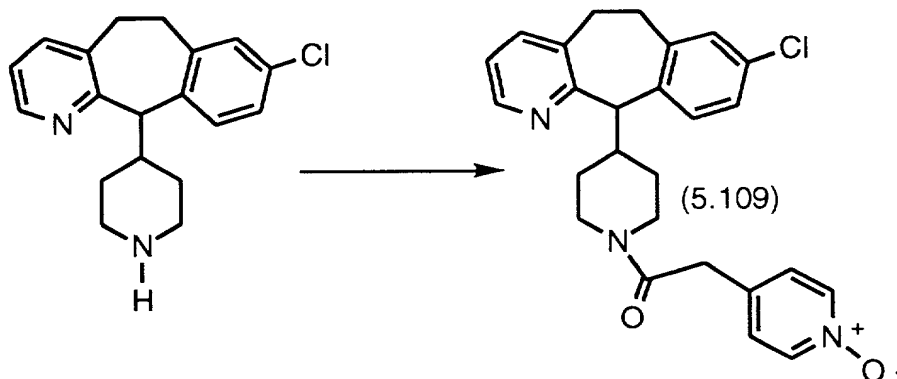


By essentially the same procedure as set forth in Example 227, but using 3-pyridyl acetic acid N-oxide (Preparative Example 9) instead of 4-pyridyl acetic acid N-oxide and 8-chloro-6,11-dihydro-11-(4-piperidiny)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine (product from Example 233A) instead of 4-(8-chloro-5,6-dihydro-11H-benzo-[5,6]cyclohepta(1,2-b)pyridin-11-ylidene)-piperidine, the title compound was obtained as a white solid (mp=117-118°C, MH<sup>+</sup>=414).

10

#### EXAMPLE 234

4-(8-CHLORO-6,11-DIHYDRO-5H-BENZO[5,6]CYCLOHEPTA(1,2-b)PYRIDIN-11-YL)-1-[(4-PYRIDINYL)ACETYL]-PIPERIDINE N1 OXIDE

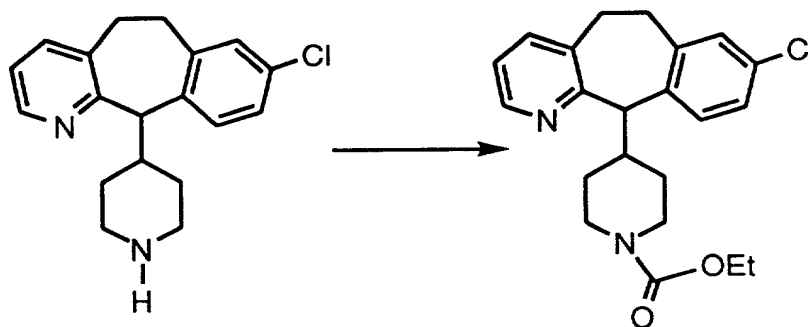


By essentially the same procedure as set forth in Example 227, but using 8-chloro-6,11-dihydro-11-(4-piperidiny)-5H-benzo[5,6]cyclohepta-[1,2-b]pyridine (product from Example 233A) instead of 4-(8-chloro-5,6-dihydro-11H-benzo-[5,6]cyclohepta(1,2-b)pyridin-11-ylidene)-piperidine (product from Preparative Example 1, step G), the title compound was obtained as a white solid (mp=125-126°C, MH<sup>+</sup>=414).

15

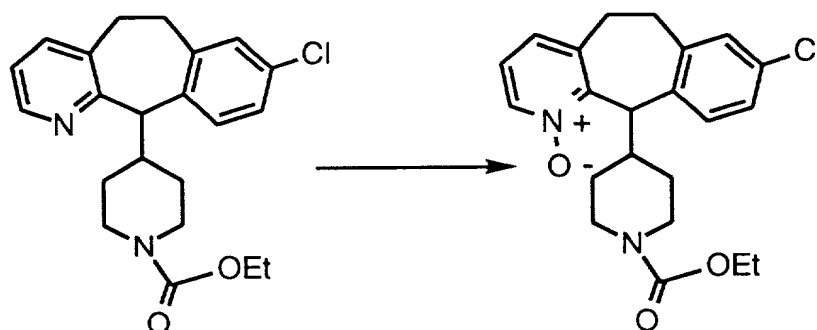
EXAMPLE 235

A. ETHYL 4-(8-CHLORO-6,11-DIHYDRO-5H-BENZO-[5,6]CYCLOHEPTA(1,2-b)PYRIDIN-11-YL)-1- PIPERIDINE-CARBOXYLATE



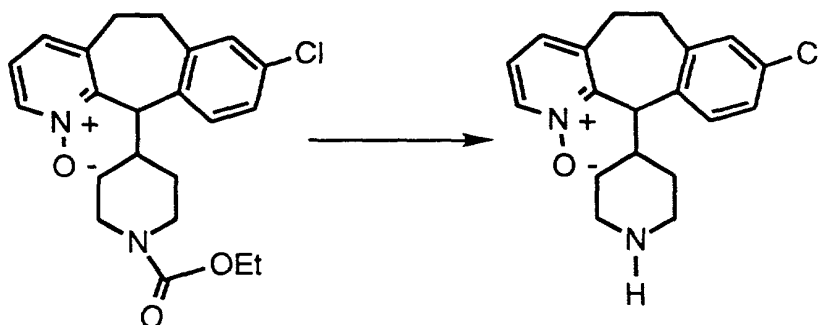
5 8-Chloro-6,11-dihydro-11-(4-piperidinyl)-5H-benzo[5,6]cyclohepta-  
[1,2-b]pyridine (product from Example 233A) (4.18g, 13mmol) was  
dissolved in toluene (175mL). Ethyl chloroformate(11.6g,110 mmol, 10.2  
10 mL) was then added and the reaction mixture was heated to ~120°C  
overnight. All volatiles were stripped off and the crude product was  
purified on silica gel column eluting with 50% EtOAc- hexanes to give the  
title compound as a white solid(MH<sup>+</sup> 385).

B. ETHYL 4-(8-CHLORO-6,11-DIHYDRO-5H-BENZO-[5,6]CYCLOHEPTA(1,2-b)PYRIDIN-11-YL)-1-PIPERIDINECARBOXYLATE  
15 N OXIDE



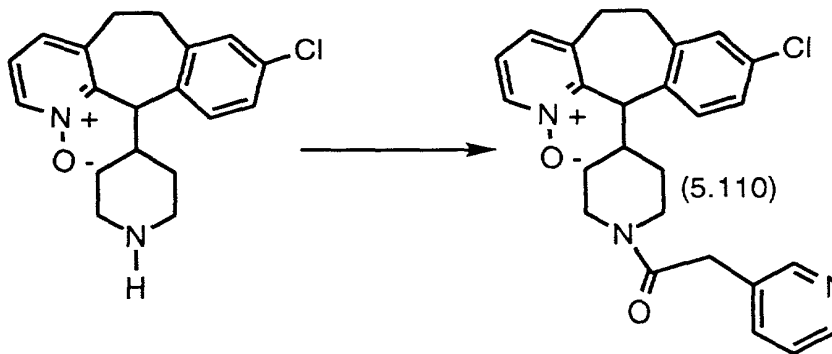
By essentially the same procedure as set forth in Example 231, but  
using ethyl 4-(8-chloro-6,11-dihydro-5H-benzo-[5,6]cyclohepta(1,2-  
b)pyridin-11-yl)-1-piperidinecarboxylate (product from Example 235A)  
20 instead of 8-chloro-11-(1-ethoxycarbonyl-4-piperidylidene)-6,11-dihydro-  
5H-benzo[5,6]cyclohepta[1,2-b]pyridine, the title compound was obtained  
as a white solid (mp= 81.7-82.5°C, MH<sup>+</sup>=400).

C. 4-(8-CHLORO-6,11-DIHYDRO-5H-BENZO-[5,6]CYCLOHEPTA(1,2-b)PYRIDIN-11-YL)-1- PIPERIDINE N OXIDE



By essentially the same procedure as set forth in Preparative Example 1 step G, but using ethyl 4-(8-chloro-6,11-dihydro-5H-benzo-[5,6]cyclohepta[1,2-b]pyridin-11-yl)-1-piperidinecarboxylate N1 oxide (product from Example 235B) instead of 8-chloro-11-(1-ethoxycarbonyl-4-piperidylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine, the title compound was obtained as a solid ( $MH^+=329$ ).

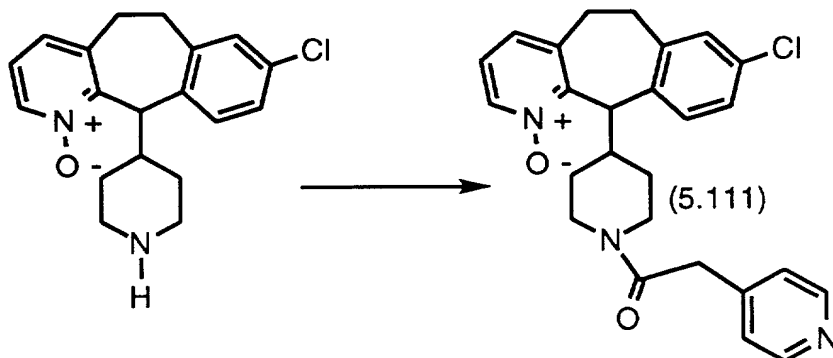
10 D. 4-(8-CHLORO-6,11-DIHYDRO-5H-BENZO[5,6]CYCLO-HEPTA(1,2-b)PYRIDIN-11-YL)-1-[(3-PYRIDINYL)ACETYL]- PIPERIDINE N4 OXIDE



By essentially the same procedure as set forth in Example 227, but using 3-pyridyl acetic acid instead of 4-pyridyl acetic acid N-oxide and 4-(8-chloro-6,11-dihydro-5H-benzo-[5,6]cyclohepta[1,2-b]pyridin-11-yl)-1-piperidine N oxide (product from Example 235C) instead of 4-(8-chloro-5,6-dihydro-11H-benzo-[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-piperidine, the title compound was obtained as a white solid (mp=61.8-62.3°C,  $MH^+=448$ ).

EXAMPLE 236

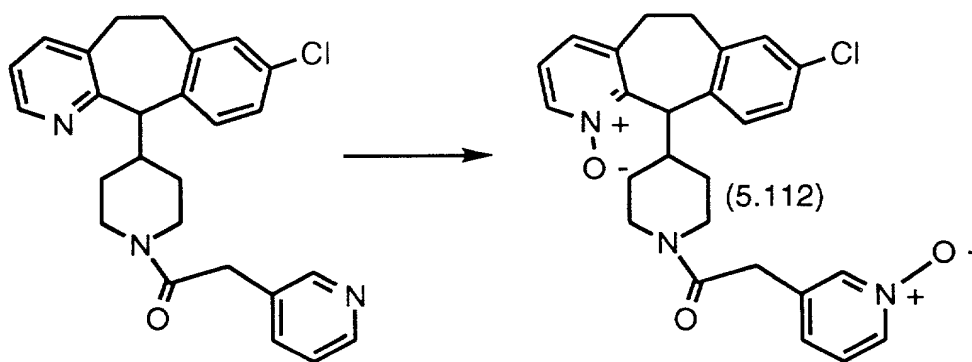
4-(8-CHLORO-6,11-DIHYDRO-5H-BENZO-[5,6]CYCLOHEPTA(1,2-b)PYRIDIN-11-YL)-1-[(4-PYRIDINYL)ACETYL]- PIPERIDINE N4 OXIDE



- 5 By essentially the same procedure as set forth in Example 227, but using 4-pyridyl acetic acid instead of 4-pyridyl acetic acid N-oxide and 4-(8-chloro-6,11-dihydro-5H-benzo-[5,6]cyclohepta(1,2-b)pyridin-11-yl)-1-piperidine N oxide (product from Example 235C) instead of 4-(8-chloro-5,6-dihydro-11H-benzo-[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-
- 10 piperidine, the title compound was obtained as a white solid (mp=116.7-117.6°C, MH<sup>+</sup>=448).

EXAMPLE 237

4-(8-CHLORO-6,11-DIHYDRO-5H-BENZO-[5,6]CYCLOHEPTA(1,2-b)PYRIDIN-11-YL)-1-[(3-PYRIDINYL)ACETYL]- PIPERIDINE N1, N4 OXIDE



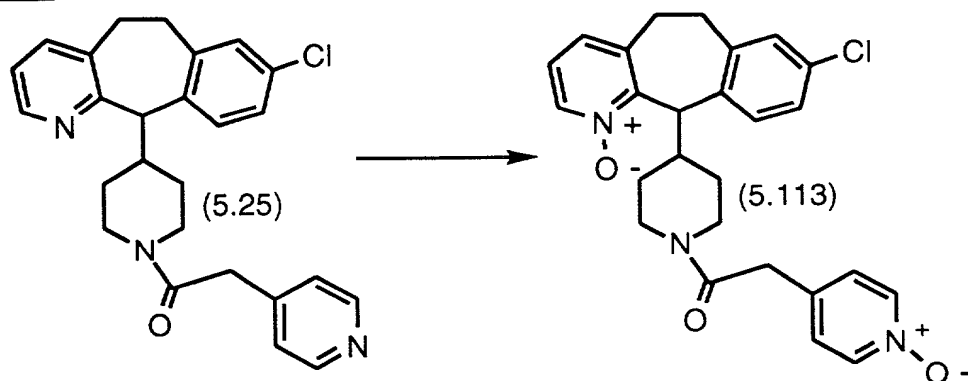
- 4-(8-Chloro-6,11-dihydro-5H-benzo-[5,6]cyclohepta(1,2-b)pyridin-11-yl)-1-[(3-pyridinyl)acetyl]-piperidine, from Example 82A, (0.5g, 1.2mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> at about -18°C. MCPBA (0.62g, 3.6 mmol) was added and the reaction stirred for 1.5 hours. The reaction mixture was extracted with 10% sodium bisulfite, 10% NaOH and then dried with MgSO<sub>4</sub>, filtered and concentrated. The crude product was
- 20

purified on silica gel eluting with 7% MeOH saturated with ammonia in  $\text{CH}_2\text{Cl}_2$  to give the title compound as a white solid (0.51g, 91% yield  $\text{MH}^+$  464).

5

EXAMPLE 238

4-(8-CHLORO-6,11-DIHYDRO-5H-BENZO-[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11-YL)-1-[(4-PYRIDINYL)ACETYL]-PIPERIDINE N1, N4 OXIDE



10

By essentially the same procedure as set forth in Example 237, but using 4-(8-chloro-6,11-dihydro-5H-benzo-[5,6]cyclohepta[1,2-b]pyridin-11-yl)-1-[(4-pyridinyl)acetyl]piperidine (product from Example 82) instead of 4-(8-chloro-6,11-dihydro-5H-benzo-[5,6]cyclohepta[1,2-b]pyridin-11-yl)-1-[(3-pyridinyl)acetyl]piperidine, the title compound was obtained as a

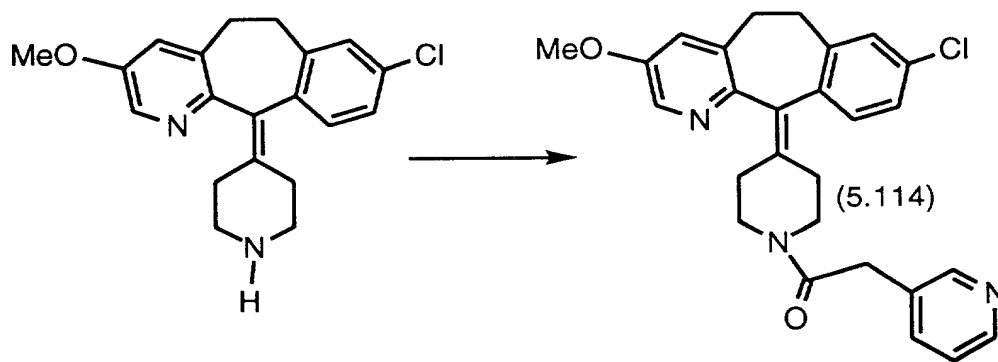
15

white solid (mp=85-85.6 °C,  $\text{MH}^+$ =464).

EXAMPLE 239

4-(8-CHLORO-3-METHOXY-5,6-DIHYDRO-11H-BENZO[5,6]-CYCLOHEPTA[1,2-b]PYRIDIN-11YLIDENE)-1-[(3-PYRIDINYL)ACETYL]-PIPERIDINE

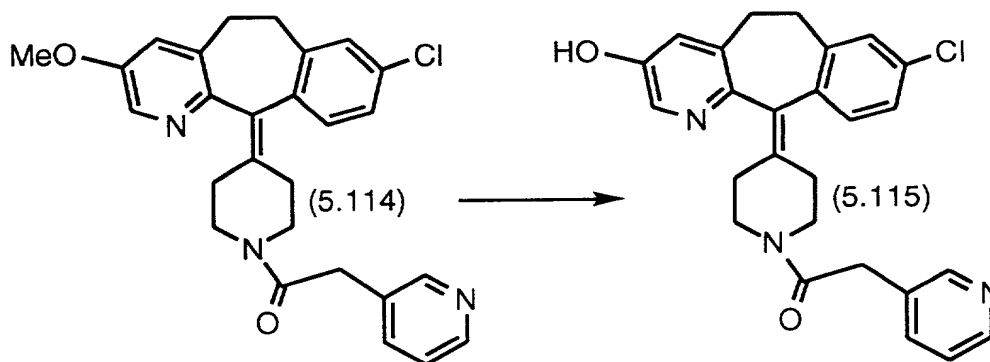
20



By essentially the same procedure as set forth in Example 180, but using 8-chloro-3-methoxy-11-(4-piperidylidene)-6,11-dihydro-5H-benzo[5,6]-cyclohepta[1,2-b]pyridine (Preparative Example 20) instead of 3,8-dichloro-11-(1-acetyl-4-piperidylidene)-6,11-dihydro-5H-benzo[5,6]-cyclohepta[1,2-b]pyridine the title compound was obtained as a white solid ( $MH^+$  460).

#### EXAMPLE 240

10 4-(8-CHLORO-3-HYDROXY-5,6-DIHYDRO-11H-BENZO[5,6]-CYCLOHEPTA[1,2-b]PYRIDIN-11-YLIDENE)-1-[(3-PYRIDINYL)-ACETYL]-PIPERIDINE

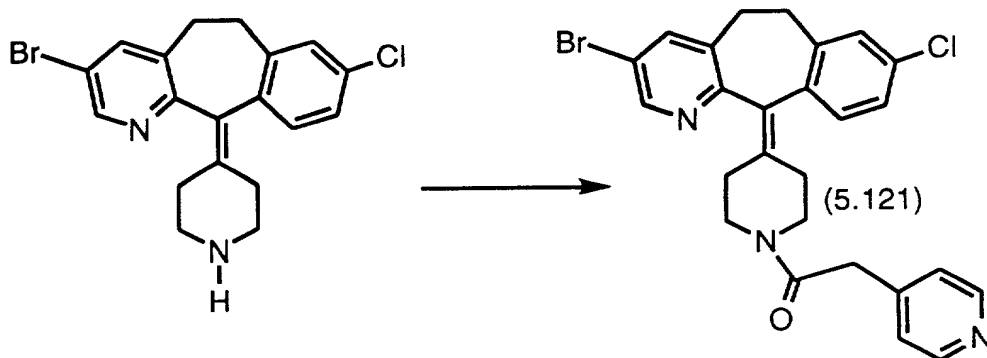


15 4-(8-Chloro-3-methoxy-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-1-[(3-pyridinyl)acetyl]piperidine (0.24g, 0.54 mmol) (Example 239) was dissolved in  $CH_2Cl_2$  at  $0^\circ C$  under nitrogen atmosphere. Bromine tribromide (0.9g, 3.6 mmol, 3.6 mL) was added and the reaction was run at room temperature for two days. The reaction mixture was concentrated and chromatographed on a silica gel column eluting with 3% MeOH saturated with ammonia in  $CH_2Cl_2$  to give an off white borate salt solid (0.14g, 61% yield,  $MH^+$  446).

20

EXAMPLE 246

1-1(4-PYRIDINYLACETYL)-4-[3-BROMO8-CHLORO5-6-DIHYDRO-11H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11YLIDENE]-PIPERIDINE

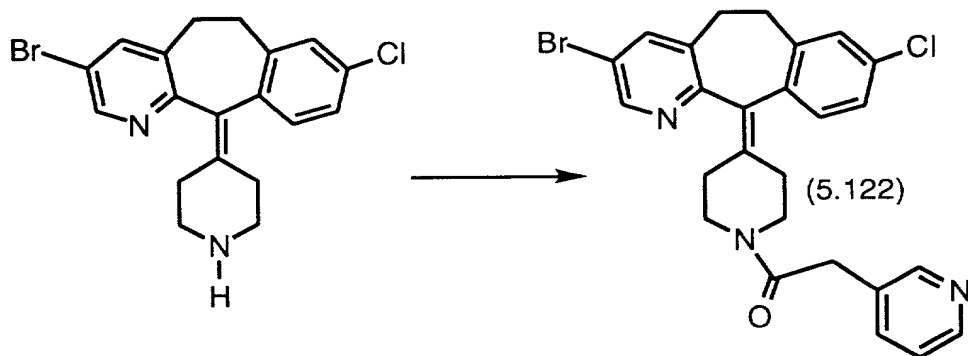


5 By essentially the same procedure as set forth in Example 180 but using 4-(3-bromo-8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta(1,2-b]pyridin-11-ylidene)-piperidine instead of 4-(3,8-dichloro-5,6-dihydro-11H-benzo-[5,6]cyclohepta(1,2-b]pyridin-11-ylidene)-piperidine, the title compound was obtained as a glassy solid (  $MH^+$  508).

10

EXAMPLE 247

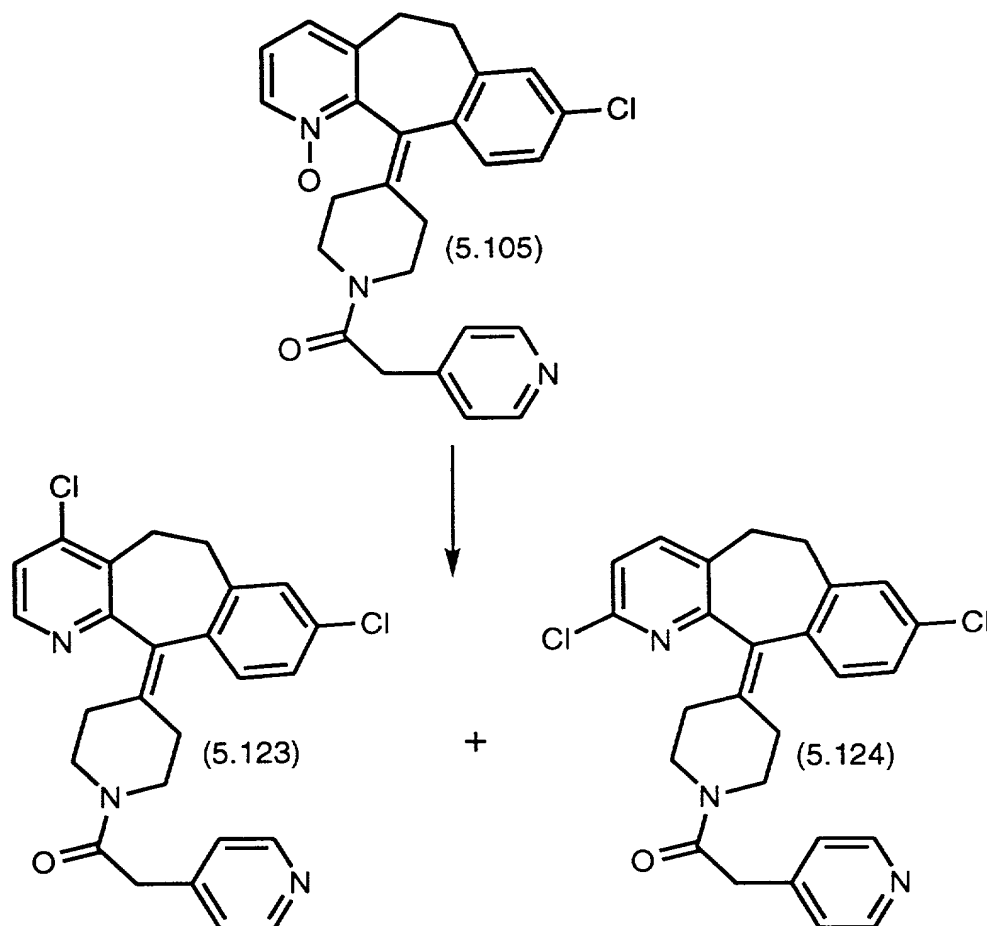
1-1(3-PYRIDINYLACETYL)-4-[3-BROMO8-CHLORO5-6-DIHYDRO-11H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11YLIDENE]-PIPERIDINE



15 By essentially the same procedure as set forth in Example 180, but using 4-(3-bromo-8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta(1,2-b]pyridin-11-ylidene)-piperidine instead of 4-(3,8-dichloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-piperidine and 3-pyridyl acetic acid instead of 4-pyridyl acetic acid, the title compound was  
20 obtained as a white solid (mp=92-93°C  $MH^+$  508).

EXAMPLE 248

4-[4,8-DICHLORO-5,6-DIHYDRO-11H-BENZO[5,6]CYCLOHEPTA-  
[1,2-b]PYRIDIN-11-YLIDENE]-1-(4-PYRIDINYLALETYL)-PIPERIDINE and  
4-[2,8-DICHLORO-5,6-DIHYDRO-11H-BENZO[5,6]CYCLOHEPTA-  
5 [1,2-b]PYRIDIN-11-YLIDENE]-1-(4-PYRIDINYLALETYL)-PIPERIDINE

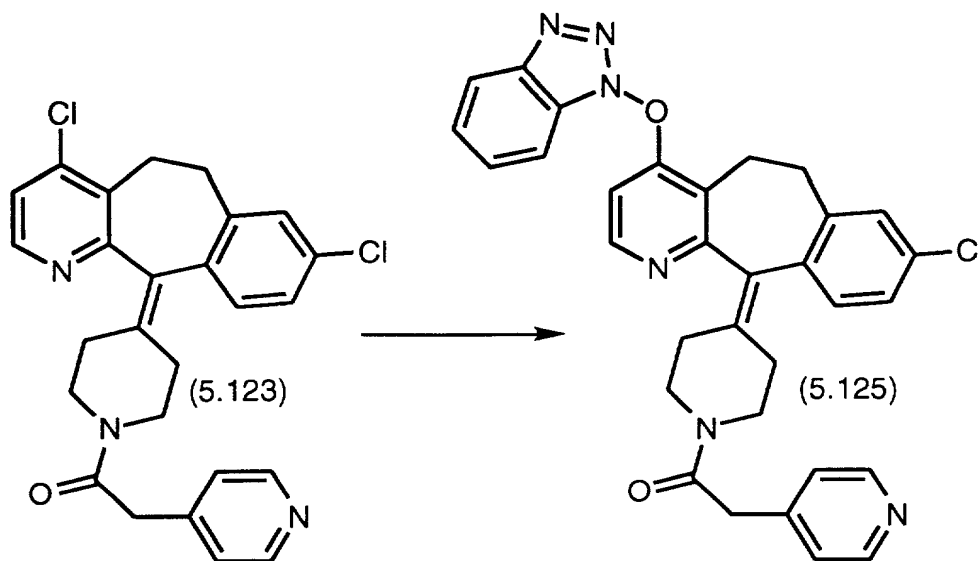


A solution of the title compound from Example 230 (1.7 grams) and phosphorous oxychloride (21 mL) dissolved in chloroform (12 mL) was stirred at reflux for 1 hour. Concentration *in vacuo* provided a residue which was diluted with CH<sub>2</sub>Cl<sub>2</sub> and washed with saturated aqueous sodium bicarbonate and brine. The organic phase was dried over anhydrous MgSO<sub>4</sub>, concentrated *in vacuo*, and purified by flash column chromatography (silica gel) using 2% MeOH-CH<sub>2</sub>Cl<sub>2</sub> to afford the title 4,8-dichloro compound (0.34 grams, 20% yield, mp 84-91 °C, MH<sup>+</sup> 464) and the title 2,8-dichloro compound (0.18 grams, 11% yield, mp 163.8-164.6 °C, MH<sup>+</sup> 464).



EXAMPLE 249

4-[4-[(1H-BENZOTRIAZOL-1-YL)OXY]-8-CHLORO-5,6-DIHYDRO-11H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11-YLIDENE]-1-(4-PYRIDINYLACETYL)-PIPERIDINE



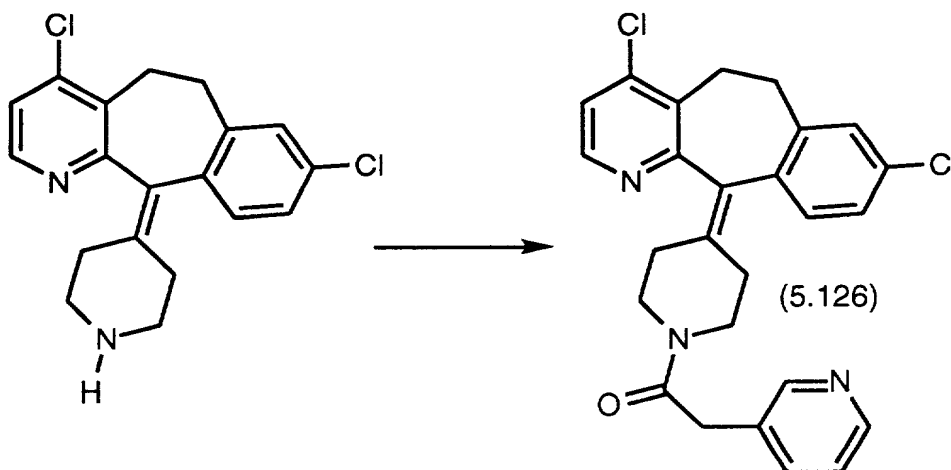
5

A mixture of the 4,8-dichloro compound from Example 248 (0.5 grams), HOBT hydrate (0.4 grams) and anhydrous DMF (20 mL) was stirred at 25°C under N<sub>2</sub> for 5 days. The mixture was concentrated *in vacuo*, diluted with CH<sub>2</sub>Cl<sub>2</sub>, and washed with 1N aqueous NaOH. The organic phase was dried over anhydrous MgSO<sub>4</sub>, concentrated *in vacuo* and purified by flash column chromatography (silica gel) using 3-5% MeOH-CH<sub>2</sub>Cl<sub>2</sub> to give the title compound (0.58 grams, 96%, mp 98.6-101.6 °C, MH<sup>+</sup> 563).

10

EXAMPLE 250

4-[4,8-DICHLORO-5,6-DIHYDRO-11H-BENZO[5,6]CYCLO-  
HEPTA[1,2-b]PYRIDIN-11-YLIDENE]-1-(3-PYRIDINYLACETYL)-  
PIPERIDINE



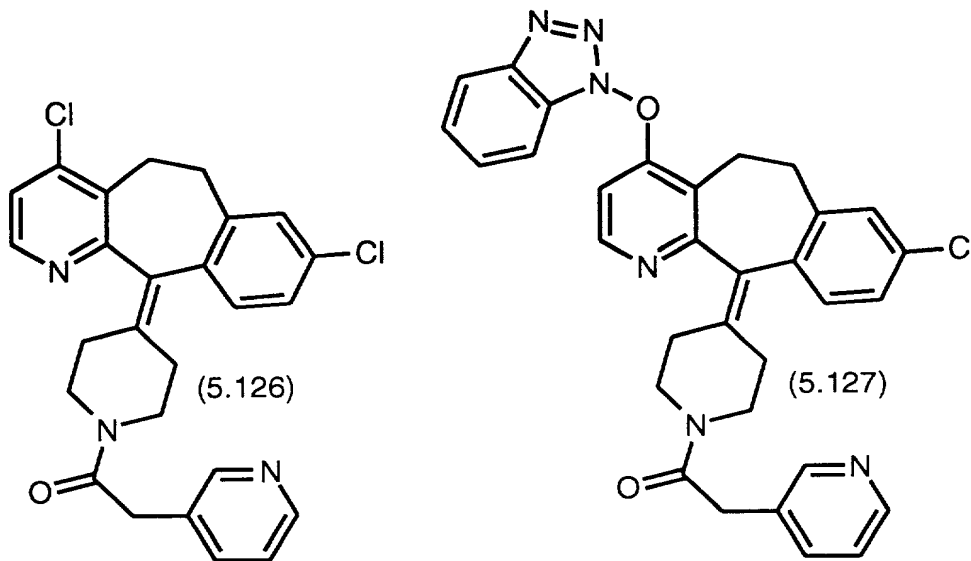
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A mixture of the 4,8-dichloro product from Preparative Example 28 (1.91 grams), 3-pyridylacetic acid hydrochloride (2.1 grams), DEC (1.6 grams), 4-methylmorpholine (1.4 mL) and anhydrous DMF (100 mL) was stirred at 25 °C overnight. Concentration *in vacuo* provided a residue which was diluted with CH<sub>2</sub>Cl<sub>2</sub> and water. The organic phase was dried over anhydrous MgSO<sub>4</sub> and concentrated *in vacuo* to provide the title compound (2.2 grams, 87%, mp 59.8-63.5 °C, MH<sup>+</sup> 464).

10

EXAMPLE 251

4-[4-[(1H-BENZOTRIAZOL-1-YL)OXY]-8-CHLORO-5,6-DIHYDRO-11H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11-YLIDENE]-1-(3-PYRIDINYLACETYL)-PIPERIDINE



5

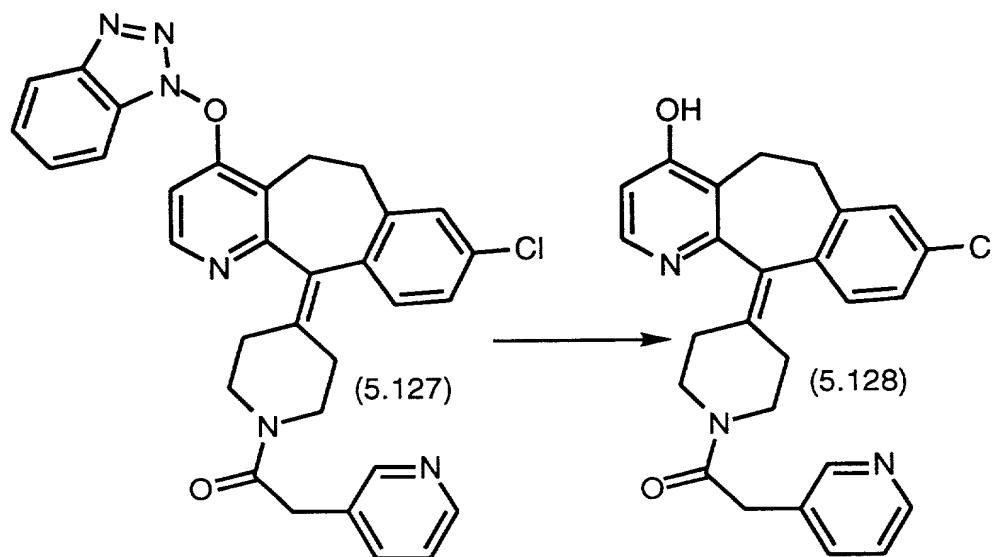
The 4,8-dichloro compound from Example 250 (0.8 grams) was added to a solution of HOBT (1.2 grams) and sodium hydride (0.14 grams, 60% in mineral oil) in anhydrous dimethyl-formamide (60 mL). The resulting solution was irradiated with a 200 W lamp while stirring at 25°C for 60 hours. The solution was poured into 1N aqueous NaOH while stirring and an additional 400 mL of water was added to the resulting mixture. Filtration provided a solid which was washed with water several times. The solid was dissolved in CH<sub>2</sub>Cl<sub>2</sub>-acetone, dried over anhydrous MgSO<sub>4</sub>, and concentrated in vacuo to provide the title compound (0.87 grams, 90%, mp = 120-122°C, MH<sup>+</sup> 563).

10

15

EXAMPLE 252

4-[4-HYDROXY-8-CHLORO-5,6-DIHYDRO-11H-BENZO[5,6]-  
CYCLOHEPTA[1,2-b]PYRIDIN-11-YLIDENE]-1-(3-PYRIDINYLACETYL)-  
PIPERIDINE



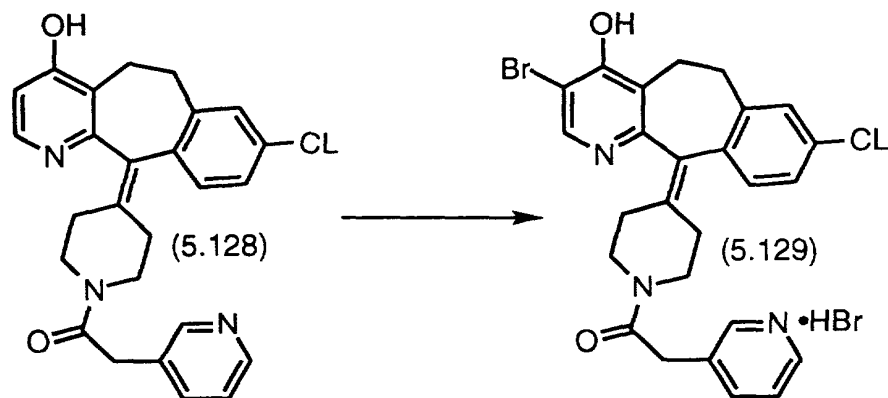
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To a solution of the title compound from Example 251 (0.8 grams) and glacial acetic acid (30 mL) was added zinc dust (0.4 grams). After stirring at 25°C for 18 hour, the mixture was filtered through celite and the filtrate concentrated *in vacuo*. The residue was diluted with EtOAc, washed with saturated aqueous sodium bicarbonate and brine. The organic layer was separated, dried over MgSO<sub>4</sub> and concentrated *in vacuo* to give the title compound (Yield 0.346 grams, 58%, MH<sup>+</sup> 446).

10

EXAMPLE 253

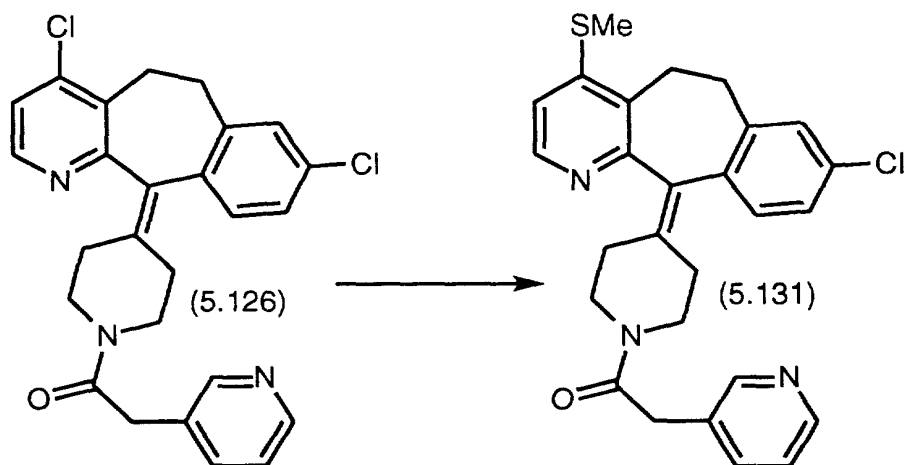
4-[3-BROMO-4-HYDROXY-8-CHLORO-5,6-DIHYDRO-11H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11-YLIDENE]-1-(3-PYRIDINYLAACETYL)-PIPERIDINE



5 To a solution of the title compound from Example 252 (0.19 grams) and glacial acetic acid (4 mL) was added a 0.7 M bromine-acetic acid solution (0.7 mL) at 25°C under N<sub>2</sub>. After 10 minutes, water was added and the resulting solid was filtered and washed with water several times  
10 and dried to give the title compound (0.18 grams, 71%, MH<sup>+</sup> 526).

EXAMPLE 255

4-[8-CHLORO-4-(METHYLTHIO)-5,6-DIHYDRO-11H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11-YLIDENE]-1-(3-PYRIDINYLAACETYL)-PIPERIDINE



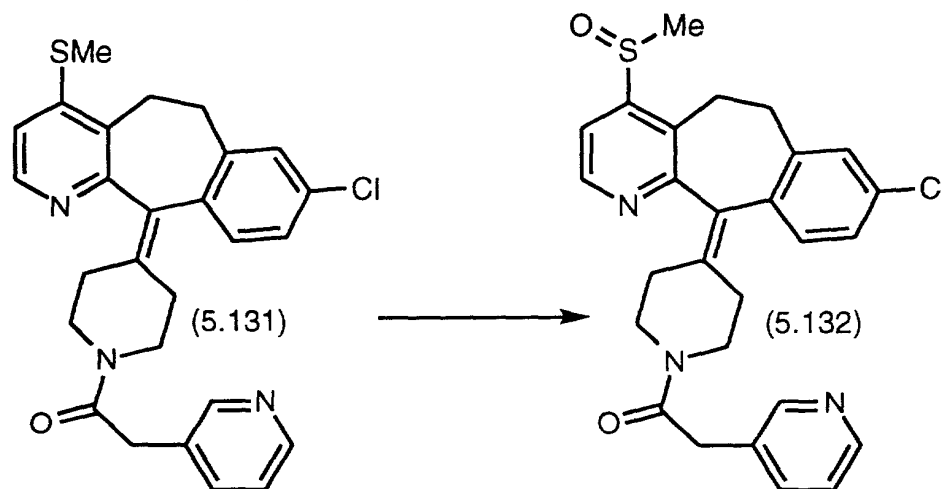
A mixture of the title compound from Example 250 (0.26 grams), sodium methylthiolate (0.06 grams) and anhydrous DMF (10 mL) was stirred while being irradiated with a 200 W lamp for 1 hour. After stirring  
20 an additional 12 hours at room temperature without irradiation, the mixture

was concentrated *in vacuo*, diluted with  $\text{CH}_2\text{Cl}_2$ , and washed with 1N aqueous NaOH and brine. The organic phase was dried over anhydrous  $\text{MgSO}_4$  and concentrated *in vacuo* to afford the title compound as a white foam (0.3 grams, 100%,  $\text{MH}^+$  476).

5

EXAMPLE 256

4-[8-CHLORO-4-(METHYLSULFINYL)-5,6-DIHYDRO-11H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11-YLIDENE]-1-(3-PYRIDINYLAACETYL)-PIPERIDINE



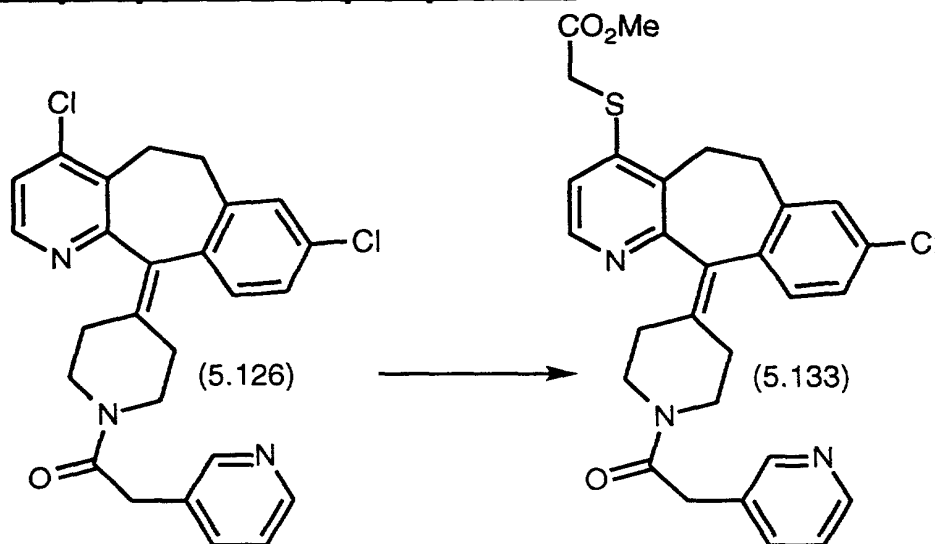
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To the title compound from Example 255 (0.18 grams) dissolved in anhydrous THF (10 mL) was added 30% aqueous hydrogen peroxide (3 mL) and the resulting solution was stirred for 12 hours at 73°C. The solution was concentrated *in vacuo*, diluted with  $\text{CH}_2\text{Cl}_2$ , and washed with water. The organic phase was dried over anhydrous  $\text{MgSO}_4$  and concentrated *in vacuo* to afford the title compound after preparative plate chromatography (silica gel) using 3% MeOH- $\text{CH}_2\text{Cl}_2$  (0.04 grams, 26%,  $\text{MH}^+$  492).

15

EXAMPLE 257

METHYL [[8-CHLORO-6,11-DIHYDRO-11-[1-[1-OXO-2-(3-PYRIDINYL)ETHYL]-4-PIPERIDINYLDENE]-5H-BENZO[5,6]CYCLO-HEPTA[1,2-b]PYRIDIN-4-YL]THIO]ACETATE



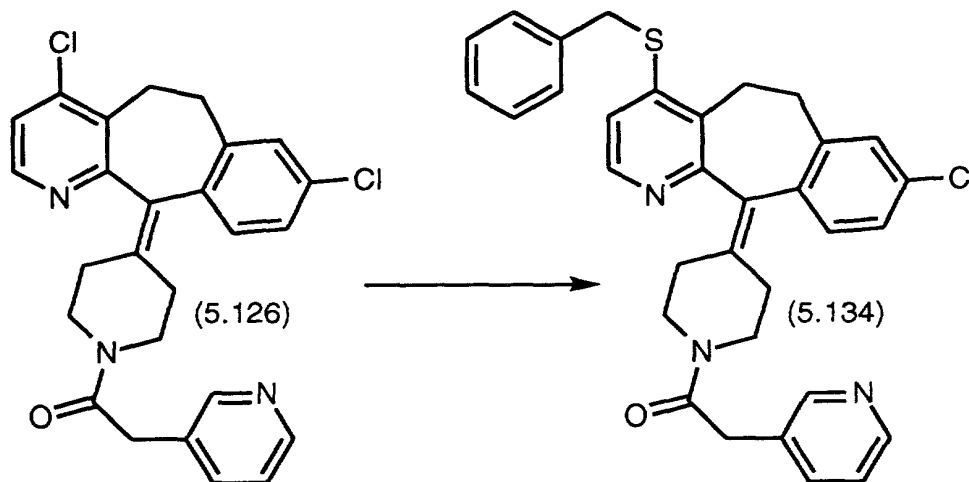
5

A mixture of the title compound from Example 250 (0.26 grams), sodium hydride (0.08 grams, 60% in mineral oil), methyl thioglycolate (0.19 mL) and anhydrous DMF (15 mL) was stirred while being irradiated with a 200 W lamp for 16 hours. The mixture was diluted with MeOH, concentrated *in vacuo*, diluted with CH<sub>2</sub>Cl<sub>2</sub> and water, and washed with 1N aqueous NaOH and brine. The organic phase was dried over anhydrous MgSO<sub>4</sub> and concentrated *in vacuo* and the residue purified by preparative plate chromatography (silica gel) using 3% MeOH-CH<sub>2</sub>Cl<sub>2</sub> to afford the title compound (0.05 grams, 15%, MH<sup>+</sup> 534).

15

EXAMPLE 258

4-[8-CHLORO-5,6-DIHYDRO-4-(PHENYLMETHYLTHIO)-11H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11-YLIDENE]-1-(3-PYRIDINYLALETYL)-PIPERIDINE



5

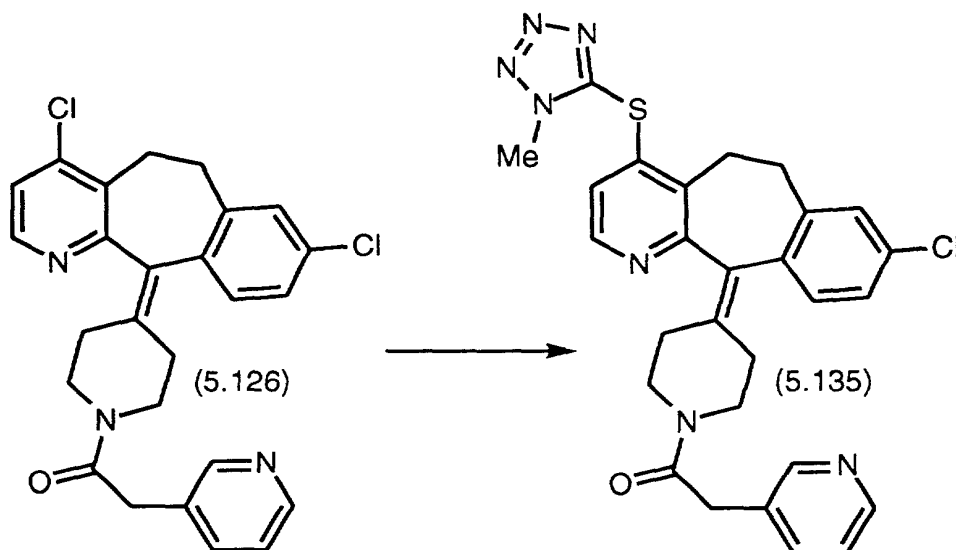
A mixture of the title compound from Example 250 (0.25 grams), sodium hydride (0.11 grams, 60% in mineral oil), benzyl mercaptan (0.13 mL) and anhydrous DMF (15 mL) was stirred while being irradiated with a 200 W lamp for 10 days. Isolation and purification as in Example 257 provided the title compound (0.02 grams, 8%, MH<sup>+</sup> 552).

10

EXAMPLE 259

4-[8-CHLORO-5,6-DIHYDRO-4-[(2-METHYL-2H-TETRAZOL-5-YL)THIO]-11H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11-YLIDENE]-1-(3-PYRIDINYLALETYL)-PIPERIDINE

15

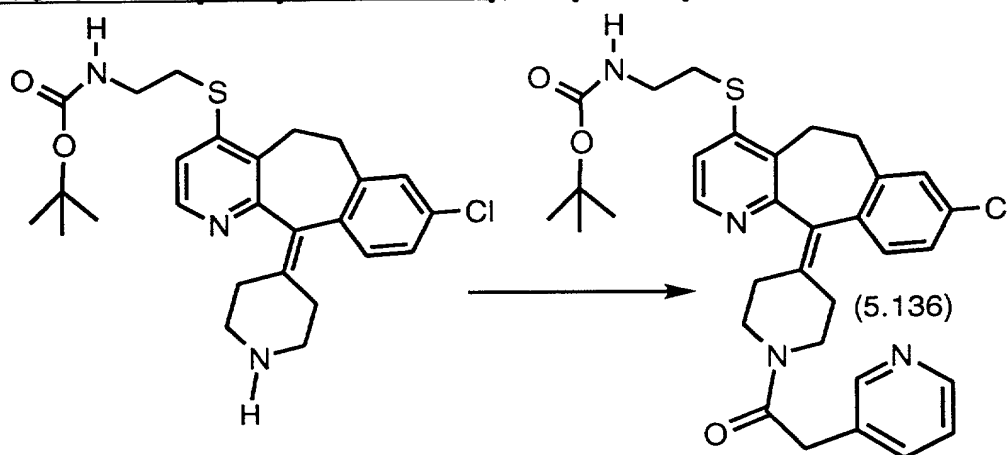




A mixture of the title compound from Example 250 (0.24 grams), 5-mercapto-1-methyltetrazole sodium salt (0.6 grams) and anhydrous DMF (10 mL) was stirred while being irradiated with a 200 W lamp for 10 days. Isolation and purification as in Example 257 provided the title compound  
 5 (0.2 grams, 68%, MH<sup>+</sup> 544).

# EXAMPLE 260

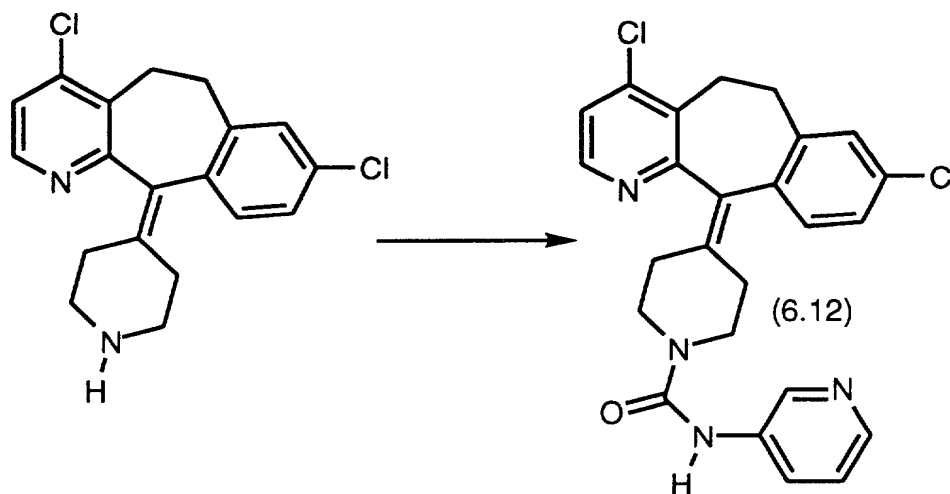
1,1-DIMETHYLETHYL [2-[[8-CHLORO-6,11-DIHYDRO-11-[1-[1-  
 OXO-2-(3-PYRIDINYL)ETHYL]-4-PIPERIDINYLDENE]-5H-BENZO[5.6]-  
 10 CYCLOHEPTA[1,2-b]PYRIDIN-4-YL]THIO]ETHYL] CARBAMATE



A mixture of the title compound from Preparative Example 32 (0.032 grams), 3-pyridylacetic acid hydrochloride (0.05 grams), DEC (0.03 grams), Et<sub>3</sub>N (0.08 mL) and anhydrous DMF (4 mL) was stirred at 25 °C  
 15 for 48 hours. Concentration *in vacuo* provided a residue which was diluted with CH<sub>2</sub>Cl<sub>2</sub> and washed with 1N aqueous NaOH. The organic phase was dried over anhydrous MgSO<sub>4</sub> and concentrated *in vacuo* to provide the title compound (0.02 grams, 50%, mp 59.8-63.5 °C, MH<sup>+</sup> 605).

EXAMPLE 261

4-(4,8-DICHLORO-5,6-DIHYDRO-11H-BENZO[5,6]CYCLO-  
HEPTA[1,2-b]PYRIDIN-11-YLIDENE)-N-(3-PYRIDYL)-1-PIPERIDINE-  
CARBOXAMIDE



5

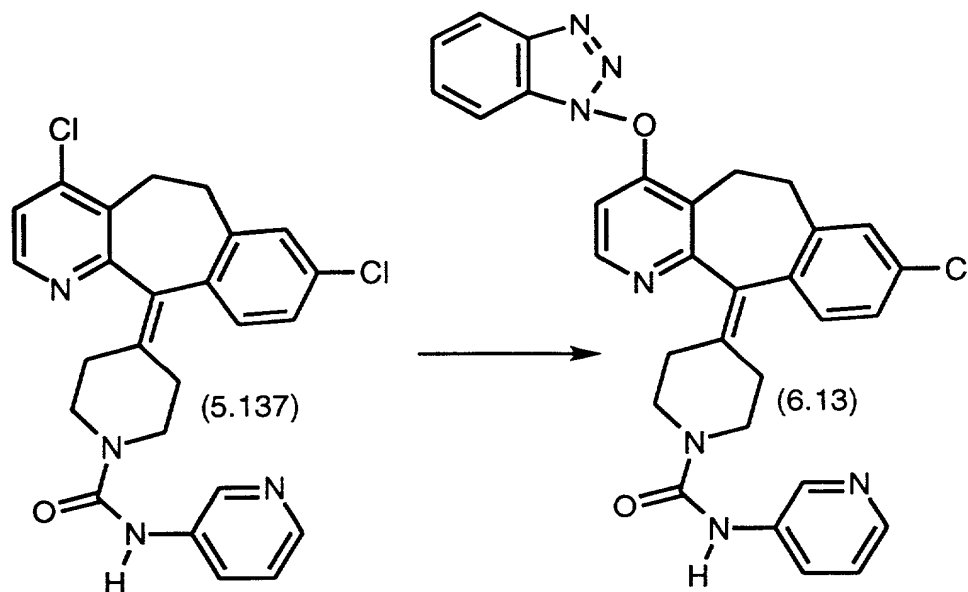
A portion of the stock solution of 3-pyridylisocyanate (32 mL) prepared as described in Preparative Example 33 was added to the 4,8-dichloro product from Preparative Example 28 (1.37 grams) and the mixture was stirred at 25°C for 4 days. The mixture was evaporated to dryness and the residue was taken up in CH<sub>2</sub>Cl<sub>2</sub> and washed with saturated aqueous sodium bicarbonate and then water. The organic solution was dried over MgSO<sub>4</sub>, filtered and evaporated to dryness. The residue was purified by flash column chromatography (silica gel) using 2% MeOH-CH<sub>2</sub>Cl<sub>2</sub> as eluent to give the title compound (Yield 1.25 grams, 70%, MH<sup>+</sup> 465).

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EXAMPLE 262

4-[4-[(1H-BENZOTRIAZOL-1-YL)OXY]-8-CHLORO-5,6-DIHYDRO-11H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11-YLIDENE]-N-(3-PYRIDYL)-1-PIPERIDINECARBOXAMIDE



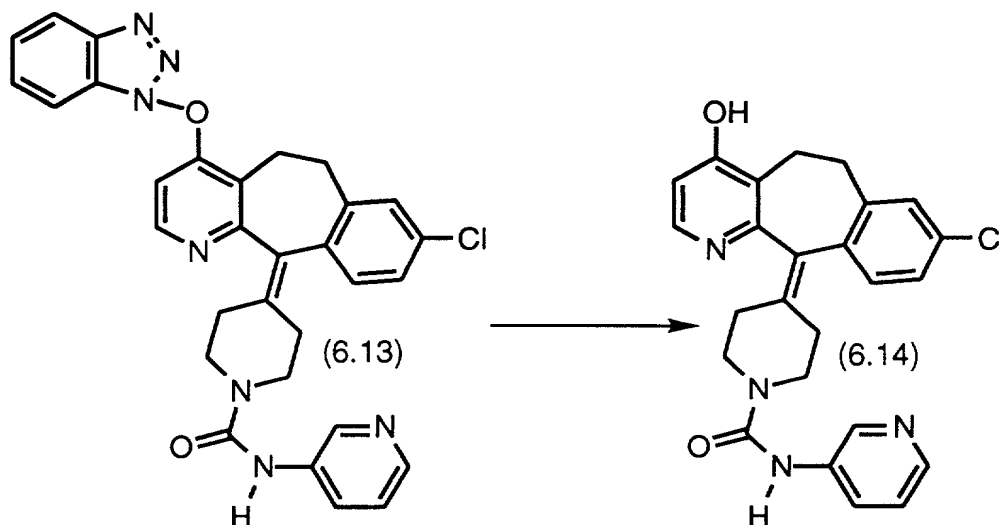
To a solution of the title compound from Example 261 (1.0 grams) in dry DMF (60 mL) was added HOBt (1.4 grams), sodium hydride (0.2 grams, 60% in mineral oil) and distilled water (0.5 mL). The solution was stirred at 25°C under nitrogen while being irradiated with a 200 Watt lamp for 20 hours. The reaction mixture was concentrated in vacuo, diluted with CH<sub>2</sub>Cl<sub>2</sub> and saturated aqueous sodium bicarbonate and after two hours, the organic phase was separated, dried over MgSO<sub>4</sub> and concentrated. Purification by flash column chromatography (silica gel) using 3-5% MeOH-CH<sub>2</sub>Cl<sub>2</sub> afforded the title compound (Yield 1.1 grams, 87%, MH+

10

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EXAMPLE 263

4-[4-HYDROXY-8-CHLORO-5,6-DIHYDRO-11H-BENZO[5,6]-  
CYCLOHEPTA[1,2-b]PYRIDIN-11-YLIDENE]-N-(3-PYRIDYL)-1-  
PIPERIDINECARBOXAMIDE



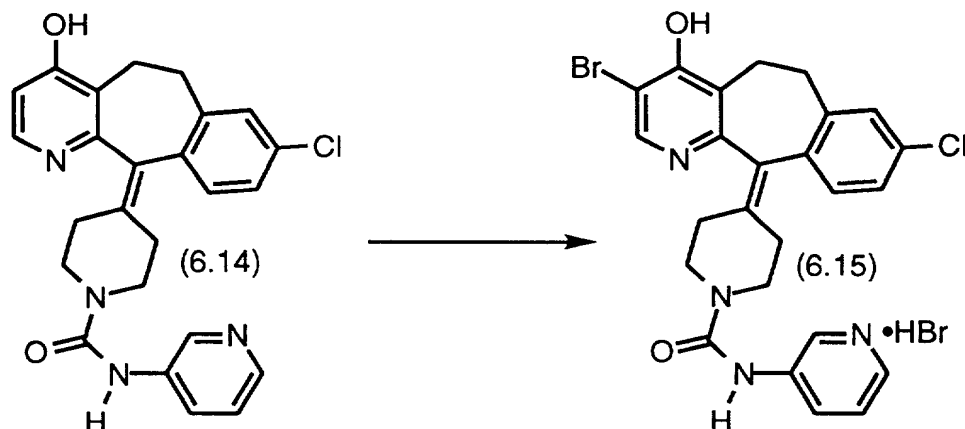
5

To a solution of the title compound from Example 262 (0.86 grams) and glacial acetic acid (20 mL) was added zinc dust (0.5 grams). After stirring at 25°C for 1.5 hours, the mixture was filtered through celite and the filtrate concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel) using 5-10% MeOH-CH<sub>2</sub>Cl<sub>2</sub> saturated with ammonium hydroxide to give the title compound (Yield 0.47 grams, 69%, MH+448).

10

EXAMPLE 264

4-[3-BROMO-4-HYDROXY-8-CHLORO-5,6-DIHYDRO-11H-  
BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11-YLIDENE]-N-(3-PYRIDYL)-  
1-PIPERIDINECARBOXAMIDE

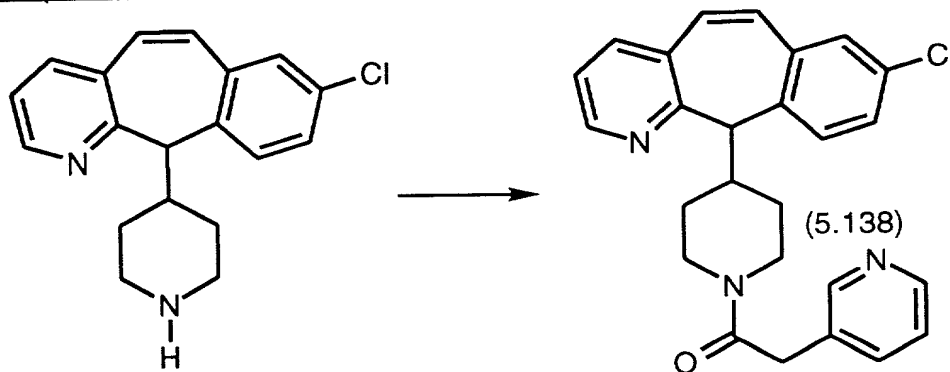


15

To a solution of the title compound from Example 263 (0.34 grams) and glacial acetic acid (10 mL) was added a 0.7 M bromine-acetic acid solution (4 mL) at 25°C under N<sub>2</sub>. After 10 minutes, water was added and the resulting solid was filtered and washed with water several times and dried to give the title compound (Yield 0.31 grams, 67%, MH<sup>+</sup> 527).

#### EXAMPLE 266

4-(8-CHLORO-5H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11-YL)-1-(3-PYRIDINYLACETYL)-PIPERIDINE



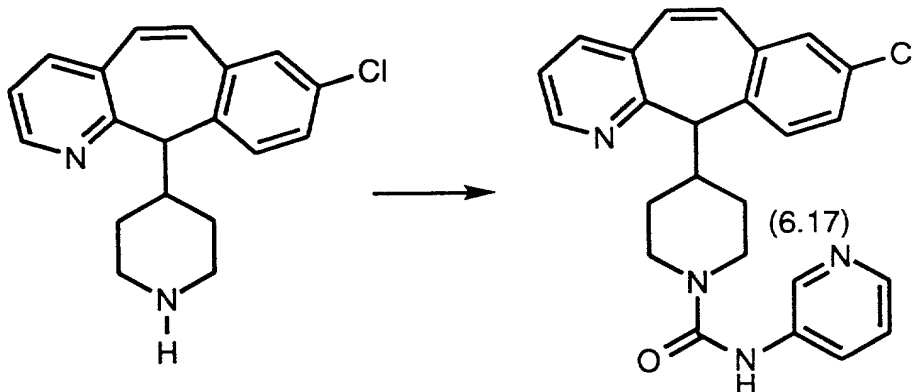
10

The title compound from Preparative Example 34C (2.0g, 6.4 mmole) was dissolved in anhydrous DMF (70 mL) and the solution was cooled with an ice bath for 30 minutes. 4-Methylmorpholine (3.3 g, 32 mmole), DEC (1.8 g, 9.7 mmole) and HOBT (0.87g 6.4 mmole) were added to the cold solution. 3-Pyridylacetic acid (0.88 g, 6.4 mmole) was added and the cooling bath removed. Stir the mixture at room temperature for 18 hours. The reaction mixture was evaporated to dryness and the residue was diluted with water (50 mL). The aqueous mixture was extracted with EtOAc and the combined extracts dried (MgSO<sub>4</sub>), filtered and evaporated. The resulting residue was purified by silica gel chromatography using a gradient of 97% CH<sub>2</sub>Cl<sub>2</sub>/ 3% MeOH saturated with ammonia to 93% dichlormethane/7% MeOH saturated with ammonia as eluent to give the title compound (0.87g MH<sup>+</sup> 430).

20

EXAMPLE 267

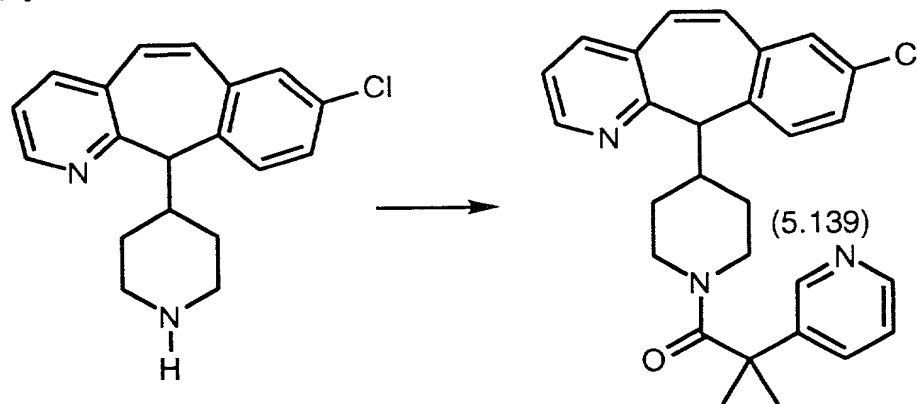
E. 4-(8-CHLORO-11H-BENZO[5.6]CYCLOHEPTA[1.2-b]PYRIDIN-11-YL)-N-(3-PYRIDINYL)-1-PIPERIDINECARBOXAMIDE



- 5 The title compound from Preparative Example 34C was treated with 3-pyridylisocyanate, similar to the procedure in Example 261, to afford the title compound ( $MH^+$  431).

EXAMPLE 268

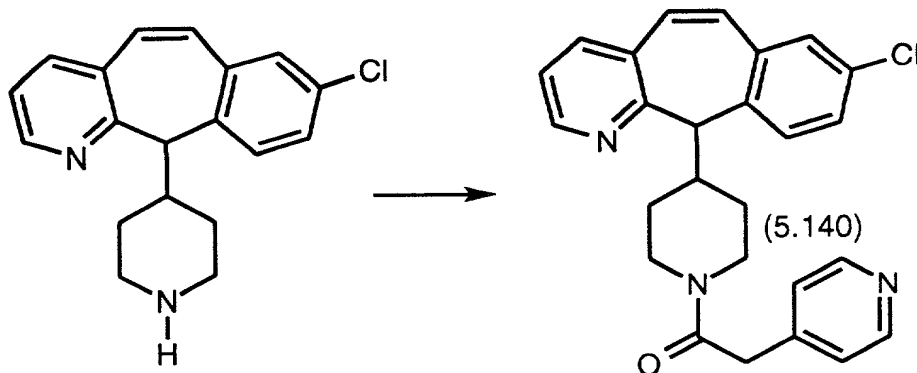
10 4-(8-CHLORO-5H-BENZO[5.6]CYCLOHEPTA[1.2-b]PYRIDIN-11-YL)-1-[2-METHYL-2-(3-PYRIDINYL)-1-OXOPROPYL]-PIPERIDINE



- 15 The title compound from Preparative Example 34C was treated as described in Example 266, using  $\alpha,\alpha$ -dimethyl-3-pyridylacetic acid (described in Preparative Example 10B) in place of 3-pyridylacetic acid, to afford the title compound ( $M^+$  458).

EXAMPLE 269

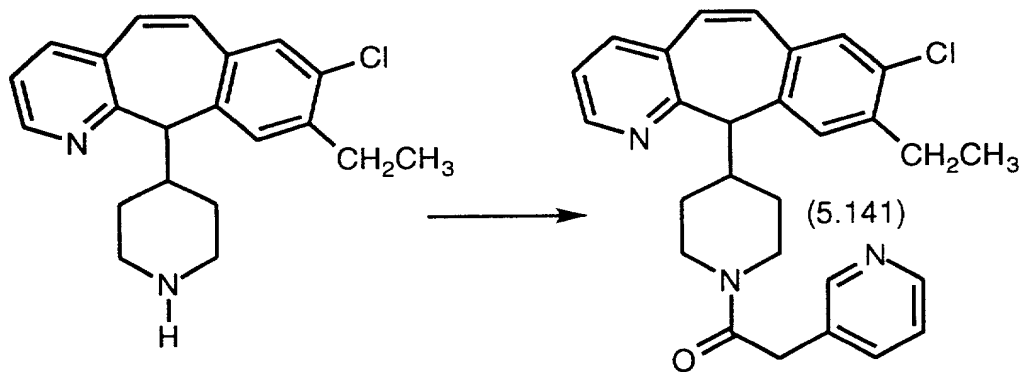
4-(8-CHLORO-5H-BENZO[5.6]CYCLOHEPTA[1.2-b]PYRIDIN-11-  
YL)-1-(4-PYRIDINYLACETYL)-PIPERIDINE



- 5 The title compound from Preparative Example 34C above was treated as described in Example 266, using 4-pyridylacetic acid in place of 3-pyridylacetic acid, to give the title compound ( $M^+$  430).

EXAMPLE 270

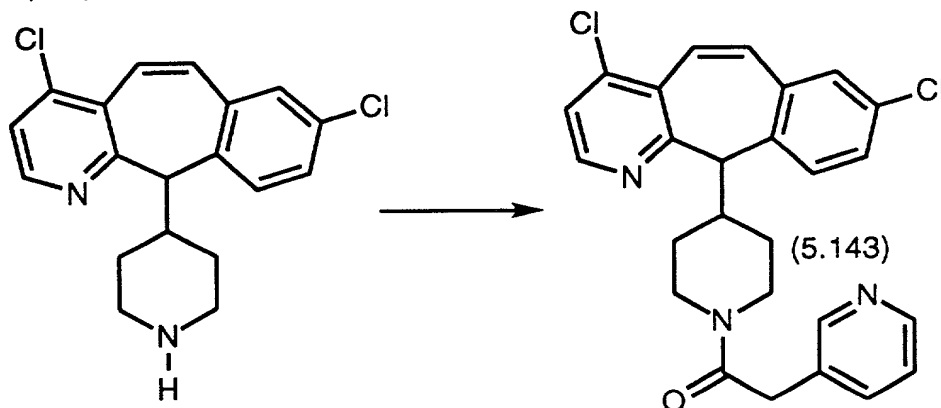
10 4-(8-CHLORO-9-ETHYL-5H-BENZO[5.6]CYCLOHEPTA-[1.2-  
b]PYRIDIN-11-YL)-1-(3-PYRIDINYLACETYL)-PIPERIDINE



- 15 The title compound from Preparative Example 2A was treated as described in Example 266 to give the title compound ( $M^+$  = 458, mp = 67.2-69.8°C).

EXAMPLE 273

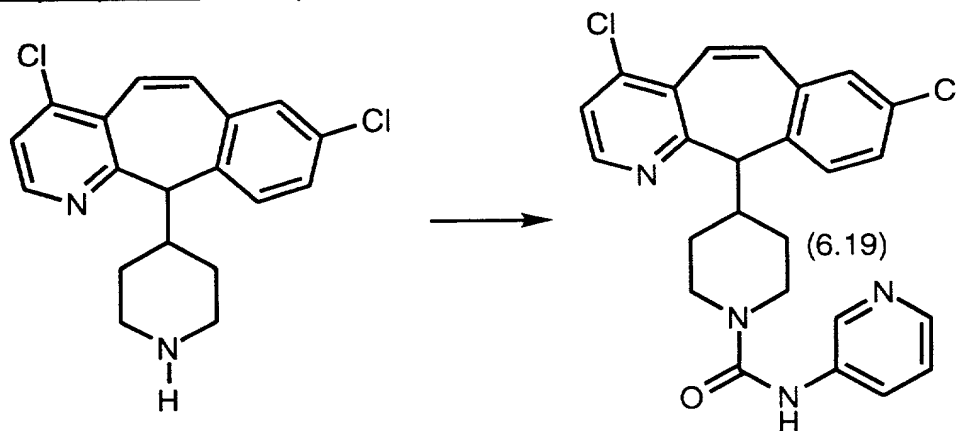
4-(4,8-DICHLORO-5H-BENZO[5,6]CYCLOHEPTA[1,2-B]PYRIDIN-11-YL)-1-(3-PYRIDINYLA-CETYL)-PIPERIDINE



- 5 The title compound from Preparative Example 36C was treated as described in Example 266 to give the title compound (mp 100.1 - 103.4°C).

EXAMPLE 274

10 4-(4,8-DICHLORO-11H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11-YL)-N-(3-PYRIDINYL)-1-PIPERIDINECARBOXAMIDE



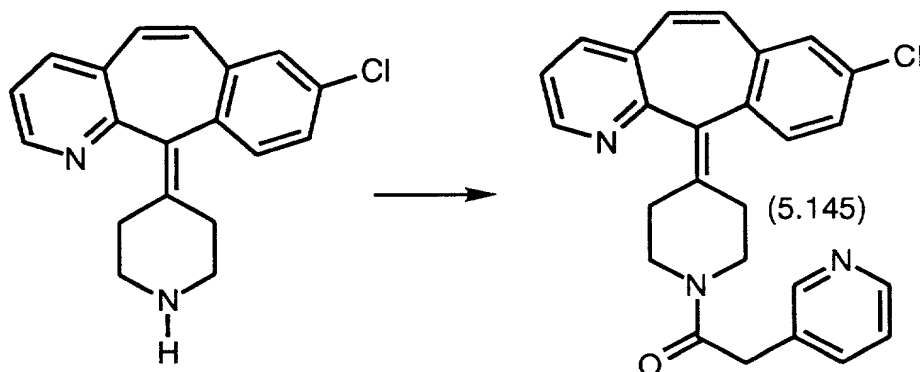
- 15 The title compound from Preparative Example 36C (0.75g, 2.17mmol) was treated with a pyridine solution of 3-pyridylisocyanate (from Preparative Example 33). The reaction mixture was evaporated to dryness and the residue dissolved in CH<sub>2</sub>Cl<sub>2</sub>. This solution was washed with saturated sodium bicarbonate solution and brine, dried (MgSO<sub>4</sub>), filtered and evaporated to give a dark syrup. The syrup was purified by silica gel chromatography using a gradient of 97% CH<sub>2</sub>Cl<sub>2</sub>/3% MeOH saturated with ammonia to 93% CH<sub>2</sub>Cl<sub>2</sub>/7% MeOH saturated with



ammonia. The title compound was obtained as a yellow solid (0.13g, 13%, M+ 465)

EXAMPLE 276

5      4-(8-CHLORO-11H-BENZO[5.6]CYCLOHEPTA[1.2-b]PYRIDIN-11YLIDENE)-1-(3-PYRIDINYLAACETYL)-PIPERIDINE

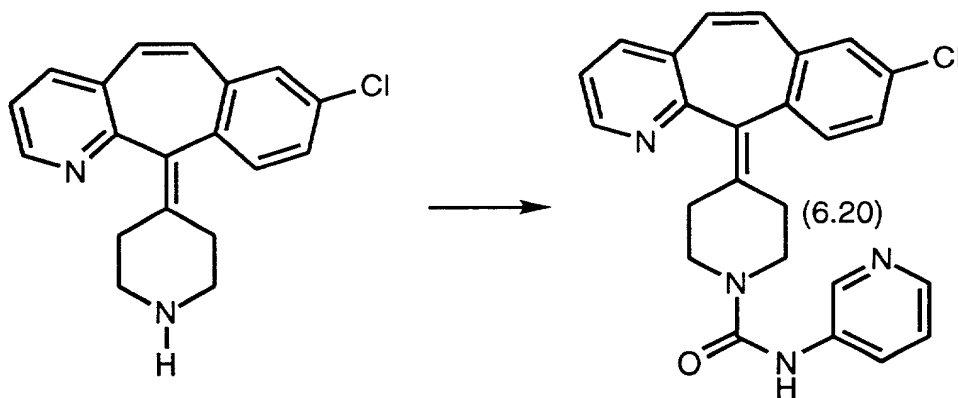


The title compound from Preparative Example 37B was treated as described in Example 266 to give the title compound (MH<sup>+</sup> 428).

10

EXAMPLE 277

10      4-(8CHLORO-11H-BENZO[5.6]CYCLOHEPTA[1.2-b]PYRIDIN-11YLIDENE)-N-(3-PYRIDINYL)-1-PIPERIDINECARBOXAMIDE

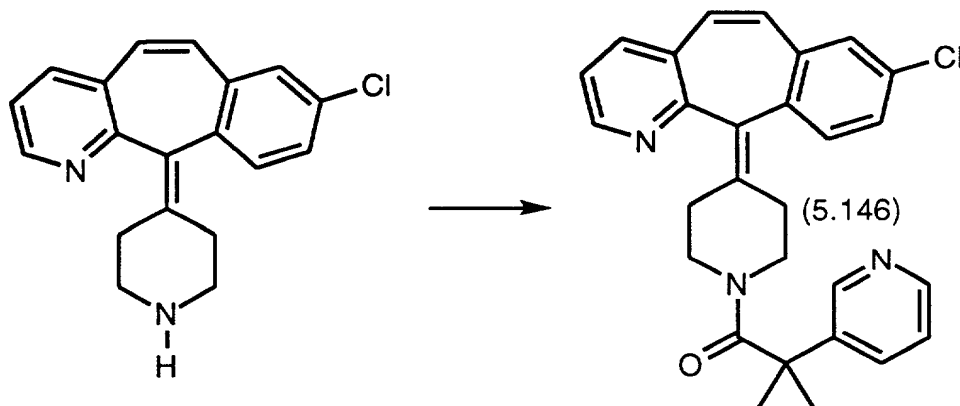


15

The title compound from Preparative Example 37B above was treated as described in Example 261 above to give the title compound (mp 95.9 - 97.6°C).

EXAMPLE 278

4-(8-CHLORO-11H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11YLIDENE)-1-[2-METHYL-2-(3-PYRIDINYL)-1-OXO-PROPYL]-PIPERIDINE



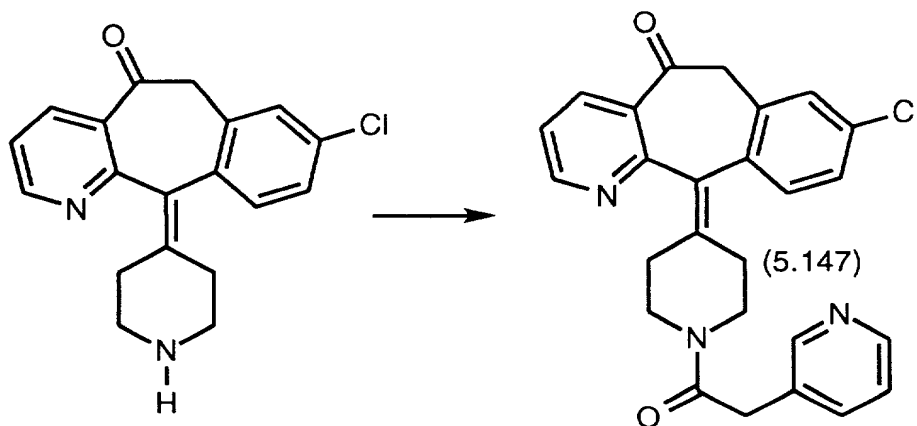
5

The title compound from Preparative Example 37B was treated as described in Example 266 using  $\alpha,\alpha$ -dimethyl-3-pyridylacetic acid (described in Preparative Example 10B) in place of 3-pyridylacetic acid, to give the title compound ( $M^+$  456).

10

EXAMPLE 279

4-(8-CHLORO-5,6-DIHYDRO-5-OXO-11H-BENZO[5,6]-CYCLO-HEPTA[1,2-b]PYRIDIN-11YLIDENE)-1-(3-PYRIDINYLACETYL)-PIPERIDINE



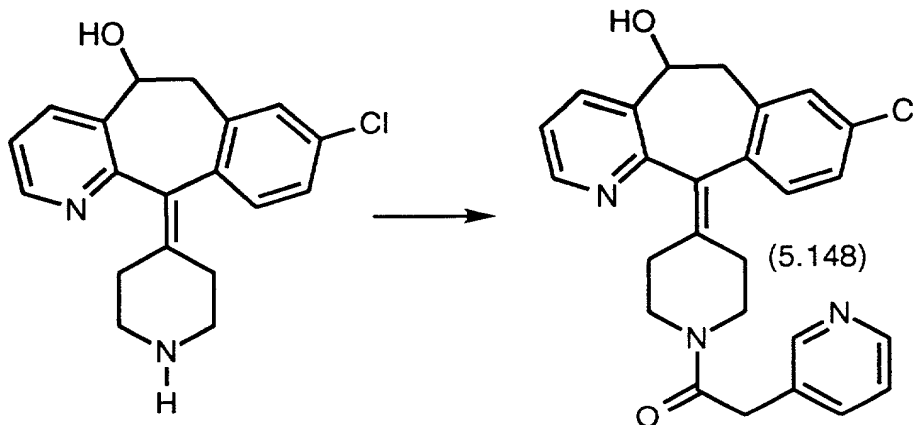
15

The preparation of the starting material for this reaction was described in *The Journal of Organic Chemistry*, **1990**, 55, pp. 3341-3350 by Piwinski, J.J.; Wong, J.K.; Chan, T.-M.; Green, M.J.; and Ganguly, A.K. The procedure described in Example 266 was followed using 8-chloro-

6,11-dihydro-11-(4-piperidinylidene)-5H-benzo[5,6]cyclohepta[1,2-b]-pyridin-5-one to give the title compound ( $M^+$  443).

### EXAMPLE 280

5      4-(8-CHLORO-5,6-DIHYDRO-5-HYDROXY-11H-BENZO-[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11YLIDENE)-1-(3-PYRIDINYL-ACETYL)-PIPERIDINE

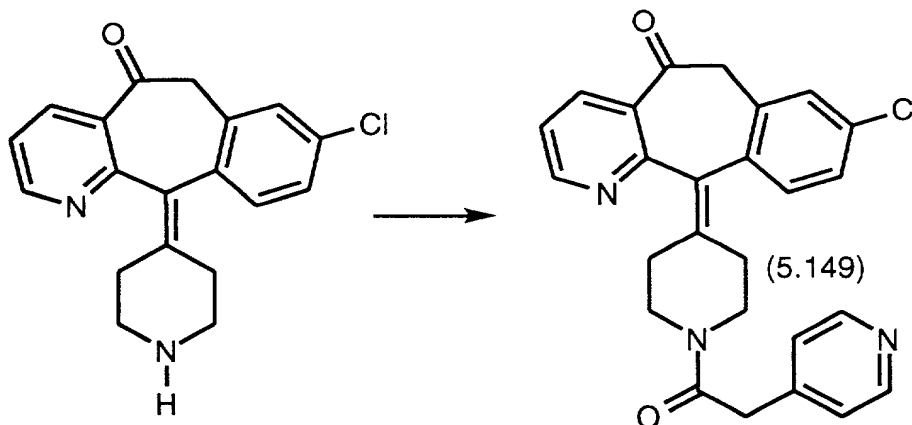


10      The preparation of the starting material for this reaction was described in *The Journal of Organic Chemistry*, **1990**, *55*, pp. 3341-3350 by Piwinski, J.J.; Wong, J.K.; Chan, T.-M.; Green, M.J.; and Ganguly, A.K. The procedure described in Example 266 was followed using 8-chloro-6,11-dihydro-5-hydroxy-11-(4-piperidinylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine to give the title compound ( $MH^+$  446).

15

### EXAMPLE 281

20      4-(8-CHLORO-5,6-DIHYDRO-5-OXO-11H-BENZO[5,6]-CYCLOHEPTA[1,2-b]PYRIDIN-11YLIDENE)-1-(4-PYRIDINYLACETYL)-PIPERIDINE



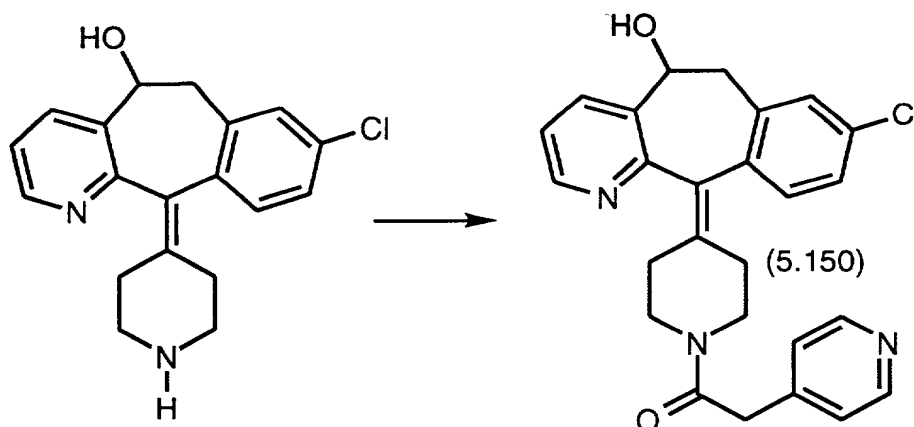
20

The procedure of Example 279 was followed with the exception that 4-pyridylacetic acid was used in place of 3-pyridylacetic acid to give the title compound ( $MH^+$  444).

5

EXAMPLE 282

4-(8-CHLORO-5,6-DIHYDRO-5-HYDROXY-11H-BENZO-[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11YLIDENE)-1-(4-PYRIDINYL-ACETYL)-PIPERIDINE



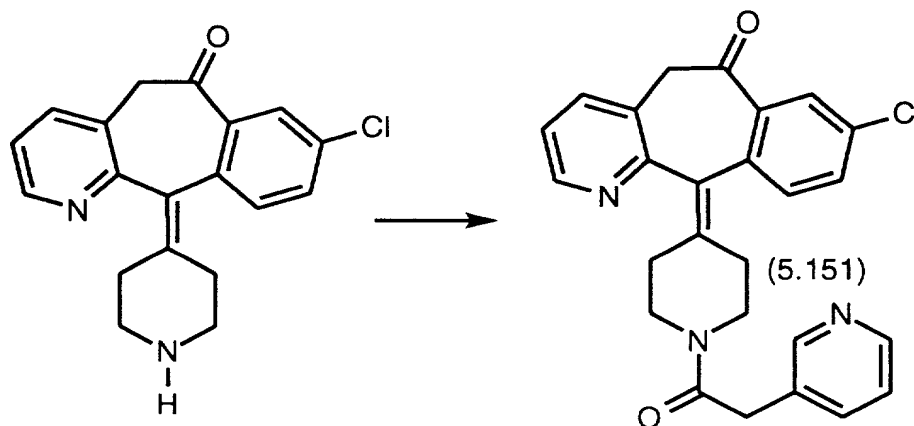
10

The procedure of Example 280 was followed with the exception that 4-pyridylacetic acid was used in place of 3-pyridylacetic acid to give the title compound ( $MH^+$  446).

EXAMPLE 283

15

4-(8-CHLORO-5,6-DIHYDRO-6-OXO-11H-BENZO[5,6]-CYCLOHEPTA[1,2-b]PYRIDIN-11YLIDENE)-1-(3-PYRIDINYLACETYL)-PIPERIDINE



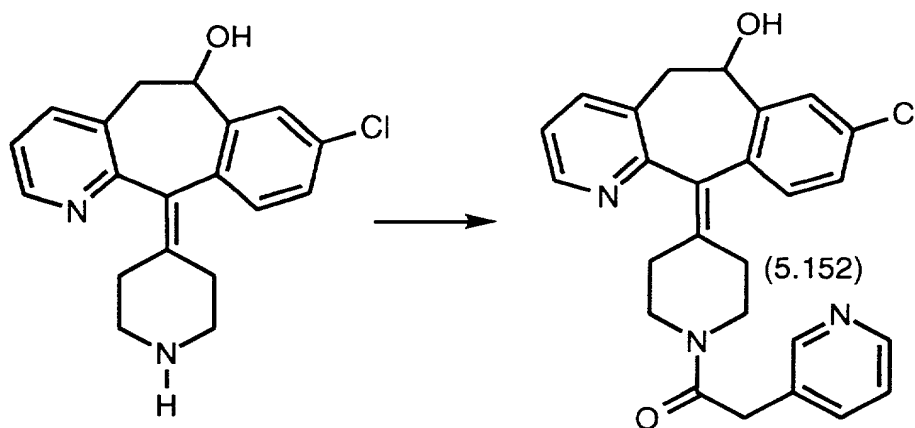
20 The preparation of the starting material for this reaction was described in *The Journal of Organic Chemistry*, **1990**, *55*, pp. 3341-3350

by Piwinski, J.J.; Wong, J.K.; Chan, T.-M.; Green, M.J.; and Ganguly, A.K. The procedure described in Example 266 was followed using 8-chloro-6,11-dihydro-11-(4-piperidinylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-6-one to give the title compound ( $M^+$  444).

5

**EXAMPLE 284**

4-(8-CHLORO-5,6-DIHYDRO-6-HYDROXY-11H-BENZO-[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11YLIDENE)-1-(3-PYRIDINYL-ACETYL)-PIPERIDINE



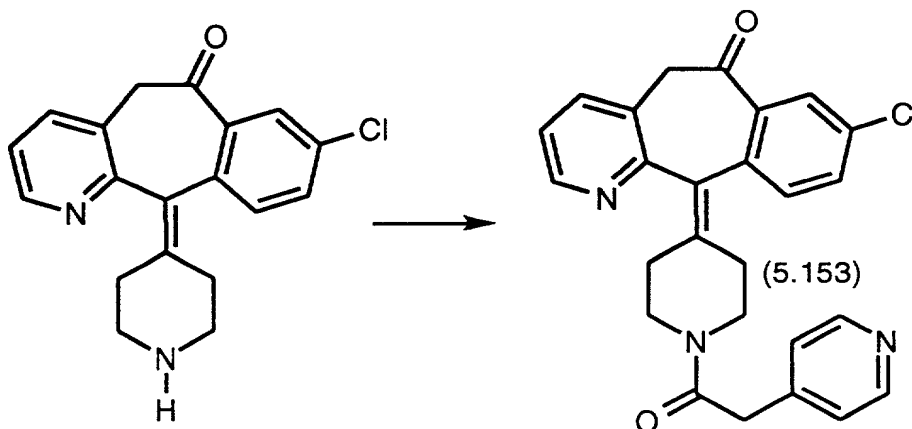
10

The preparation of the starting material for this reaction was described in *The Journal of Organic Chemistry*, **1990**, 55, pp. 3341-3350 by Piwinski, J.J.; Wong, J.K.; Chan, T.-M.; Green, M.J.; and Ganguly, A.K. The procedure described in Example 266 above was followed using 8-chloro-6,11-dihydro-6-hydroxy-11-(4-piperidinylidene)-5H-benzo[5,6]-cyclohepta[1,2-b]pyridine to give the title compound ( $MH^+$  446).

15

EXAMPLE 285

4-(8-CHLORO-5,6-DIHYDRO-6-OXO-11H-BENZO[5.6]-  
CYCLOHEPTA[1.2-b]PYRIDIN-11YLIDENE)-1-(4-PYRIDINYLACETYL)-  
PIPERIDINE



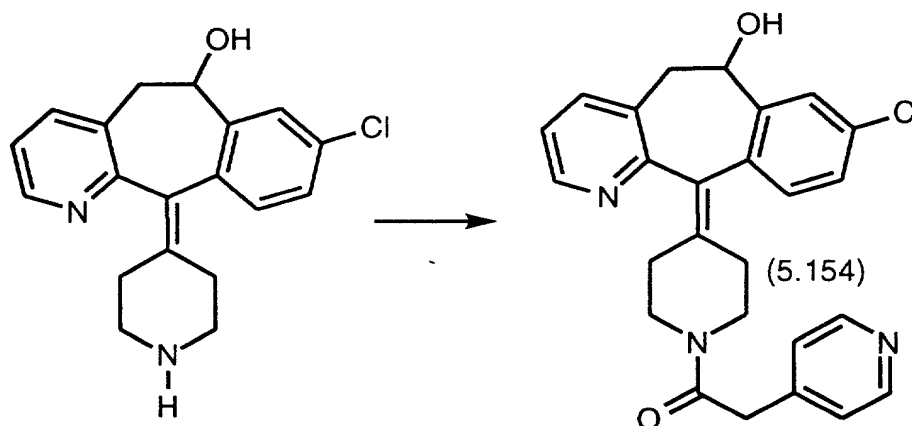
5

The procedure of Example 283 was followed with the exception that 4-pyridylacetic acid was used in place of 3-pyridylacetic acid to give the title compound ( $M^+$  444).

10

EXAMPLE 286

4-(8-CHLORO-5,6-DIHYDRO-6-HYDROXY-11H-BENZO-  
[5.6]CYCLOHEPTA[1.2-b]PYRIDIN-11YLIDENE)-1-(4-PYRIDINYL-  
ACETYL)-PIPERIDINE



15

The procedure of Example 284 was followed with the exception that 4-pyridylacetic acid was used in place of 3-pyridylacetic acid to give the title compound ( $MH^+$  446).

EXAMPLES 287, 289 AND 290

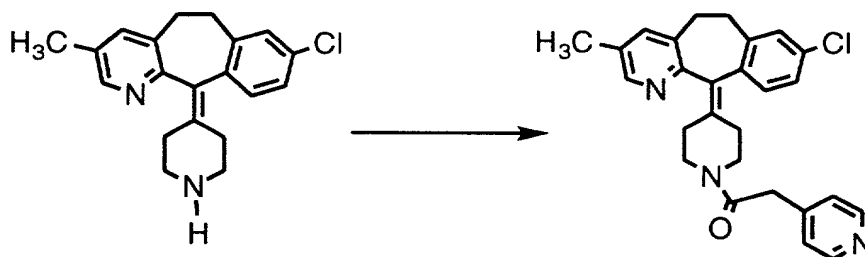
By essentially the same procedure as in Example 1, but using either (R)-(+)- $\alpha$ -methoxy- $\alpha$ -(trifluoromethyl)-phenylacetic acid (Example 290), (S)-(-)- $\alpha$ -methoxy- $\alpha$ -(trifluoromethyl)-phenylacetic acid (Example 287), or  $\alpha,\alpha$ -dimethylphenylacetic acid (Example 289), the compounds of Example 290, 287 and 289 were obtained. The structures for these compounds are in Table 7. Data for these compounds are: compound of Example 290, white solid  $MH^+$  527; compound of Example 287, white solid  $MH^+$  527; and compound of Example 289, white solid  $M^+$  457.

EXAMPLES 291, 292, 294, 313 AND 314

By essentially the same procedure as in Example 183, and using either 4-, 3-, or 2-ethoxycarbonylaminopyridine and either 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)piperidine or 8-chloro-6,11-dihydro-11-(4-piperidiny)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine (product of Example 233A), the compounds of Examples 291, 292, 294, 313 and 314 were obtained. The structures for the compounds of Examples 291, 292, and 294 are given in Table 7. The structures for the compounds of Examples 313 and 314 are given in Table 10. Data are: the compound of Example 291 was a yellow solid ( $MH^+$  431), the compound of Example 292 was an off white solid ( $MH^+$  431), the compound of Example 294 was an off white solid ( $MH^+$  431), the compound of Example 313 was a white solid ( $MH^+$  433), and the compound of Example 314 was a white solid ( $MH^+$  433).

EXAMPLE 301

1-1-(4-PYRIDINYLALETYL)-4-[3-METHYL-8-CHLORO-5,6-DIHYDRO-11H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11-YLIDENE]-PIPERIDINE



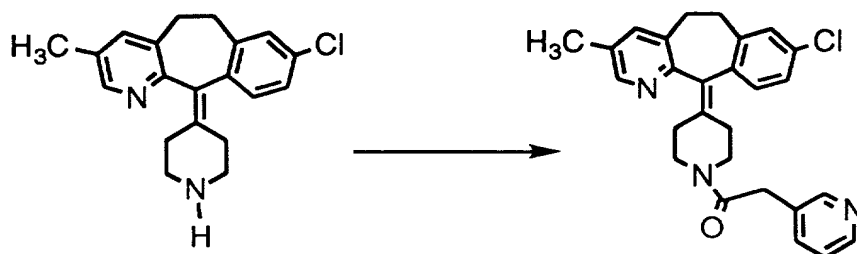
By essentially the same procedure as set forth in Example 180, but using 4-(8-chloro-3-methyl-5,6-dihydro-11-(4-piperidylidene)-11H-benzo[5,6]cyclohepta[1,2-b]pyridine (from Preparative Example 3E)

instead of 4-(3,8-dichloro-5,6-dihydro-11-(4-piperidylidene)-11H-benzo[5,6]cyclohepta[1,2-b]pyridine, the title compound was obtained as an off-white solid MH+ 444

5

EXAMPLE 303

1-1-(3-PYRIDINYLACETYL)-4-[3-METHYL-8-CHLORO-5,6-DIHYDRO-11H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11-YLIDENE]-PIPERIDINE



10

By essentially the same procedure as set forth in Example 180, but using 4-(8-chloro-3-methyl-5,6-dihydro-11-(4-piperidylidene)-11H-benzo[5,6]cyclohepta[1,2-b]pyridine (from Preparative Example 3E) instead of 4-(3,8-dichloro-5,6-dihydro-11-(4-piperidylidene)-11H-benzo[5,6]cyclohepta[1,2-b]pyridine, and 3-pyridylacetic acid instead of 4-pyridylacetic acid, the title compound was obtained as white solid MH+ 444.

15

EXAMPLE 307

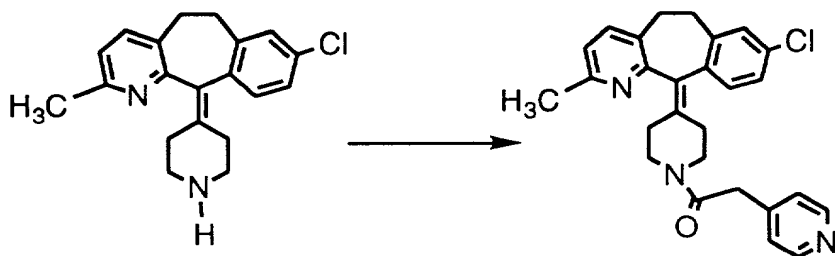
By essentially the same procedure as in Example 1, using the title compound from Preparative Example 37B, and 4-pyridylacetic acid the compound of Example 307, identified in Table 8, was obtained, MH+ 428.

20

EXAMPLE 309

1-1-(4-PYRIDINYLACETYL)-4-[2-METHYL-8-CHLORO-5,6-DIHYDRO-11H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11-YLIDENE]-PIPERIDINE

25

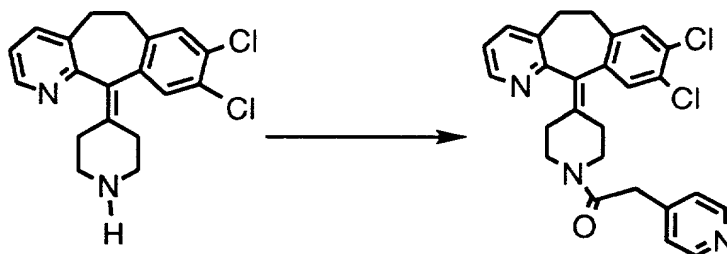




By essentially the same procedure as set forth in Example 180, but using 4-(8-chloro-2-methyl-5,6-dihydro-11-(4-piperidylidene)-11H-benzo[5,6]cyclohepta[1,2-b]pyridine (from Preparative Example 3E) instead of 4-(3,8-dichloro-5,6-dihydro-11-(4-piperidylidene)-11H-benzo[5,6]cyclohepta[1,2-b]pyridine, and 3-pyridylacetic acid instead of 4-pyridylacetic acid, the title compound was obtained as white solid MH<sup>+</sup> 444.

#### EXAMPLE 311

10 1-1-(4-PYRIDINYLACETYL)-4-[8,9 DICHLORO-5,6-DIHYDRO-11H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11-YLIDENE] - PIPERIDINE



By essentially the same procedure as set forth in Example 180, but using 4-(8,9-dichloro-5,6-dihydro-11-(4-piperidylidene)-11H-benzo[5,6]cyclohepta[1,2-b]pyridine (from Preparative Example 1H) instead of 4-(3,8-dichloro-5,6-dihydro-11-(4-piperidylidene)-11H-benzo[5,6]cyclohepta[1,2-b]pyridine, and 3-pyridylacetic acid instead of 4-pyridylacetic acid, the title compound was obtained as white solid MH<sup>+</sup> 464.

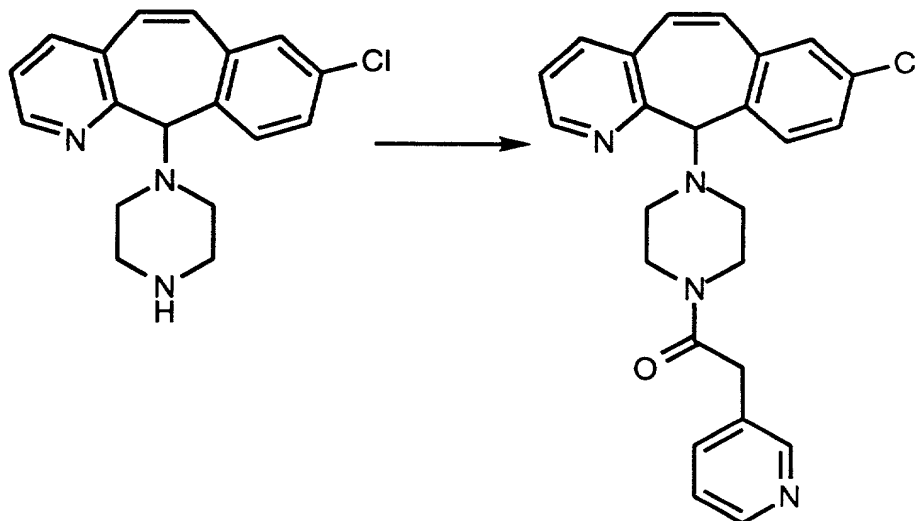
20

#### EXAMPLE 312

By essentially the same procedure as in Example 182, with the exception that 8-chloro-6,11-dihydro-11-(4-piperidiny1)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine is used instead of 8-chloro-11-(1-piperazinyl)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine, the compound of Example 312 was obtained as a white solid (MH<sup>+</sup> 432). The structure for this compound is given in Table 10.

EXAMPLE 350

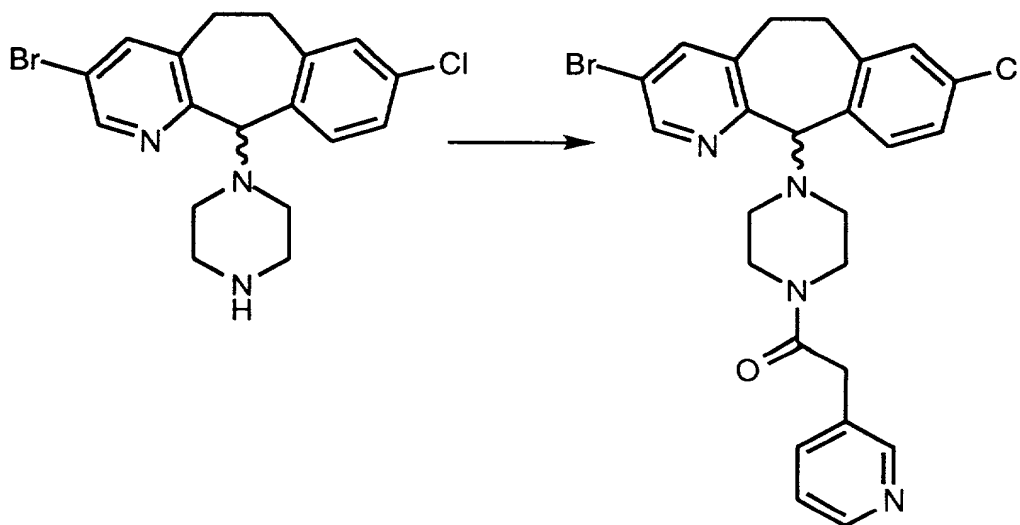
8-CHLORO-11H-BENZO[5.5]CYCLOHEPTA[1.2-b]PYRIDIN- 11-  
YLIDENE)-4-(3-PYRIDINYLACETYL)PIPERAZINE



- 5 By substituting in Example 75, 0.4g (1.28mmoles) of 8-chloro-11-  
(1-piperazinyl)-11H-benzo[5,6]cyclohepta[1,2-b]pyridine (Preparative  
Example 38) for 8-chloro-11-(1-piperazinyl)-6,11-dihydro-5H-benzo[5,6]-  
cyclohepta[1,2-b]pyridine and 0.1765g (1.28mmoles) of 3-pyridylacetic  
acid for 4-pyridylacetic acid and using the same method as described in  
10 Example 75, one obtains the title compound (0.513g, 93%, MH<sup>+</sup> 431).

EXAMPLE 351

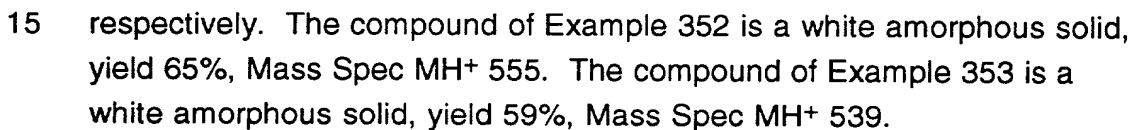
1-(3-BROMO-8-CHLORO-6,11-DIHYDRO-5H-BENZO[5.6]CYCLO-  
HEPTA[1.2-b]PYRIDIN-11-YL)-4-(3-PYRIDINYLACETYL)PIPERAZINE



5

## 10

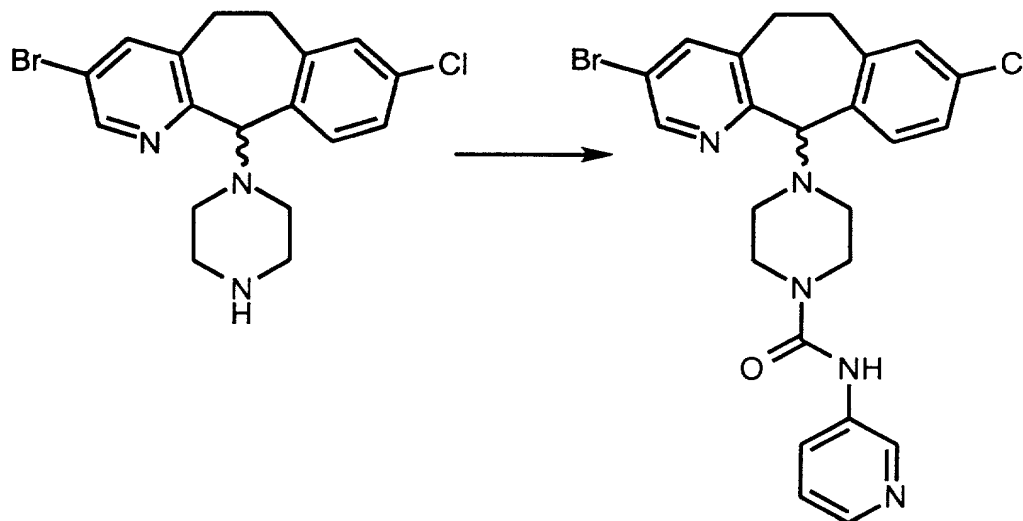
in place of 3-pyridylacetic acid, one obtains compounds of the formulas



15

EXAMPLE 354

4-(3-BROMO 8-CHLORO-6,11-DIHYDRO-5H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11-YL)-N-(3-PYRIDINYL)-1-PIPERAZINE-CARBOXAMIDE



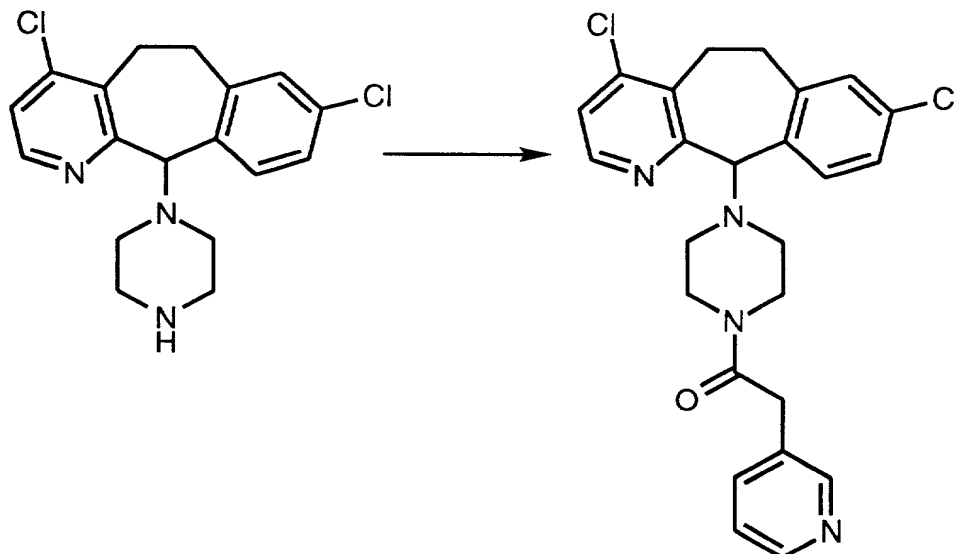
5

The title compound from Preparative Example 40 (0.37g, 0.94mmoles) was reacted with 3-ethoxycarbonylaminopyridine (Preparative Example 12) (0.123g, 0.94mmoles) under essentially the same conditions as described in Example 183, to give the title compound (0.3164g, 66%,  $MH^+$  512).

10

EXAMPLE 355

1-(4,8-DICHLORO-6,11-DIHYDRO-5H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11-YL)-4-(3-PYRIDYLACETYL) PIPERAZINE

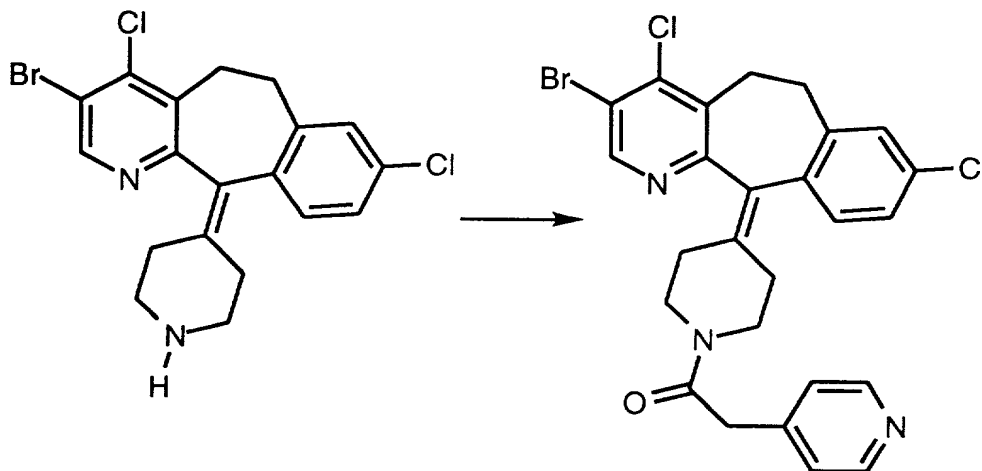


15

By substituting in Example 75, 4,8-chloro-11-(1-piperazinyl)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine (0.3g, 0.86mmoles) (Preparative Example 41) for 8-chloro-11-(1-piperazinyl)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine and 3-pyridylacetic acid (0.1181g, 0.86mmoles) for 4-pyridylacetic acid and using the method described in Example 75, one obtains the title compound (0.357g, 88%, MH<sup>+</sup> 467).

EXAMPLE 356

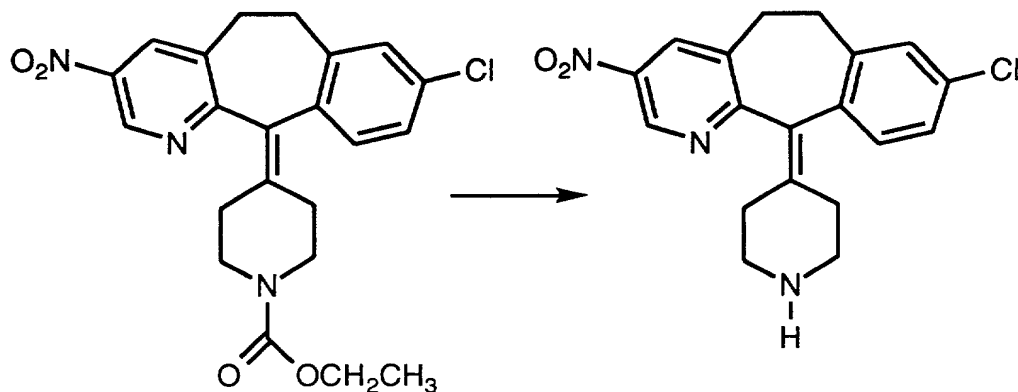
4-[3-BROMO-4,8-DICHLORO-5,6-DIHYDRO-11H-BENZO[5,6]-  
10 CYCLOHEPTA[1,2-b]PYRIDIN-11-YLIDENE]-1-(4-PYRIDINYLACETYL)-  
PIPERIDINE



A mixture of the title compound from Preparative Example 46 (0.68 grams), 4-pyridylacetic acid hydrochloride (0.60 grams), DEC (0.65  
15 grams), 4-methyl-morpholine (0.6 mL) and anhydrous DMF (20 mL) was stirred at 25°C for 48 hours. Concentration *in vacuo* provided a residue which was diluted with CH<sub>2</sub>Cl<sub>2</sub> and washed with 1 N aqueous NaOH and brine. The organic phase was dried over anhydrous MgSO<sub>4</sub> and concentrated *in vacuo* to provide a residue which was purified by flash  
20 column chromatography (silica gel) using 2-5% MeOH-CH<sub>2</sub>Cl<sub>2</sub> saturated with ammonium hydroxide to afford the title compound (0.06 grams, 7%, MH<sup>+</sup> 544).

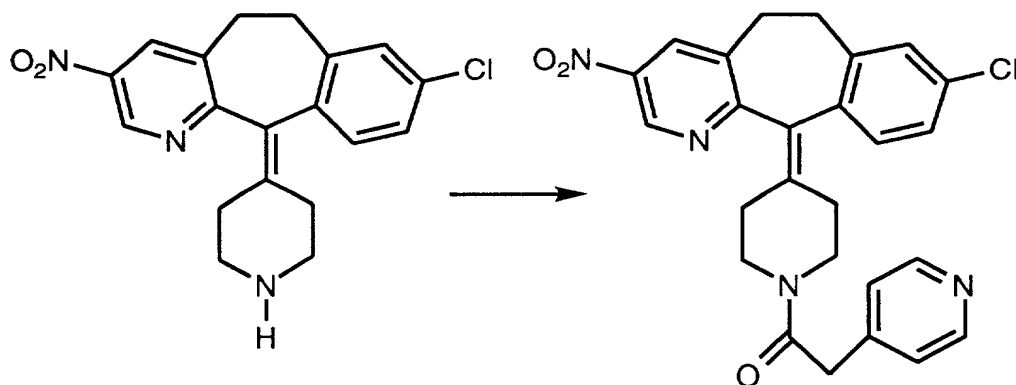
EXAMPLE 358

A. 4-(8-CHLORO-3-NITRO-5,6-DIHYDRO-11-(4-PIPERIDYLDENE)-11H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDINE.



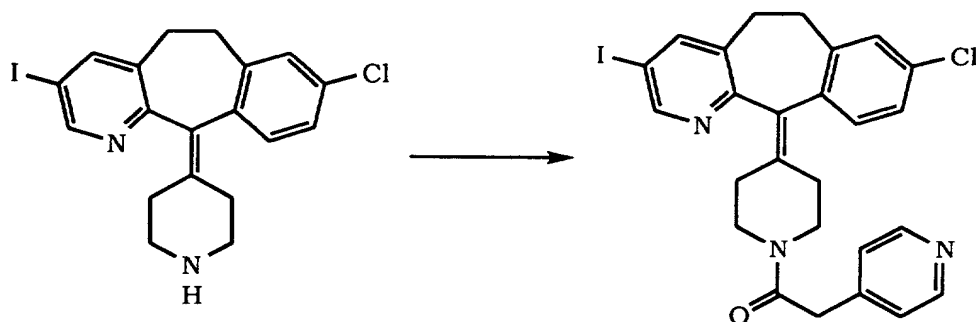
- 5 Hydrolyze the title compound of Preparative Example 47A (10.0g, mmol) by dissolving in conc. HCl (250mL) and heating to 100°C for 16h. The cooled acidic mixture was neutralized with 1M NaOH (950 mL). The mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The latter was dried over MgSO<sub>4</sub>. Filtration and concentration afforded the title compound in 99% yield as a solid. MH+ 358.

B. 1-1-(4-PYRIDINYLACETYL) -4-[3-BROMO-8-CHLORO-5,6-DIHYDRO-11H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11-YLDENE] - PIPERIDINE



- 15 By essentially the same procedure as set forth in Example 180, but using 4-(8-chloro-3-nitro-5,6-dihydro-11-(4-piperidinylidene)-11H-benzo[5,6]cyclohepta[1,2-b]pyridine instead of 4-(3,8-dichloro-5,6-dihydro-11-(4-piperidinylidene)-11H-benzo[5,6]cyclohepta[1,2-b]pyridine, the title compound was obtained as an off-white solid. Mp = 111.3-20 112.2°C, MH+ 475.

**EXAMPLE 400**

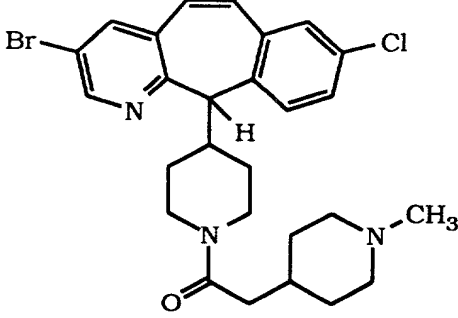
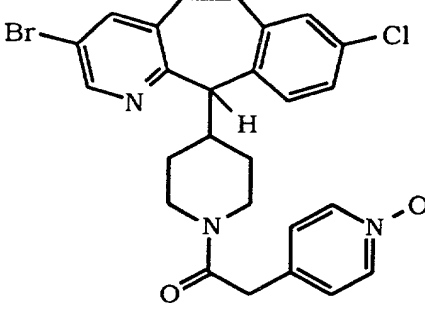
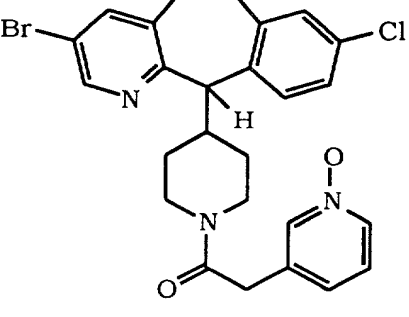


5 The product of Preparative Example 48, Step B, is reacted with 4-pyridyl acetic acid via essentially the same procedure as described in Example 180 to give the product compound (5.210).

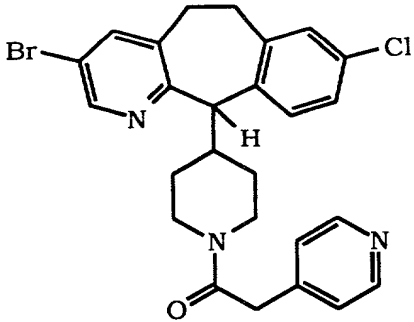
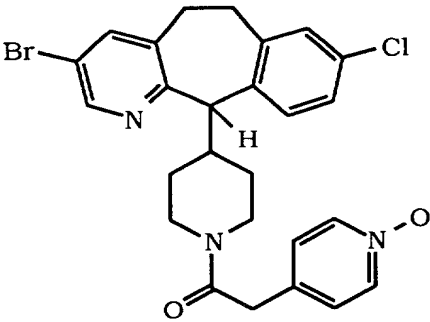
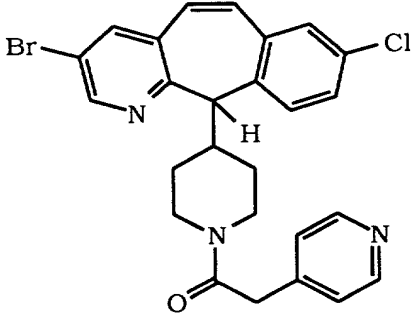
Mass Spec.:  $MH^+ = 556$

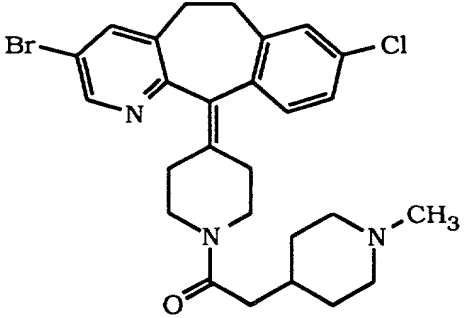
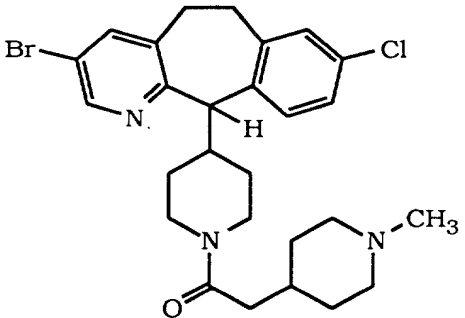
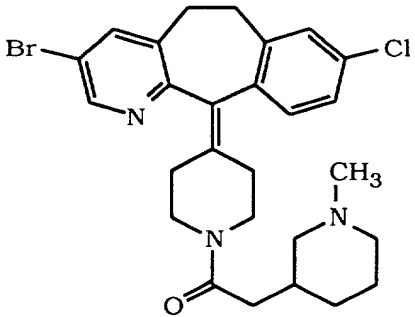
10 Using the appropriate carboxylic acid and the starting compound indicated, the following compounds were prepared via substantially the same procedure as described for Example 400:

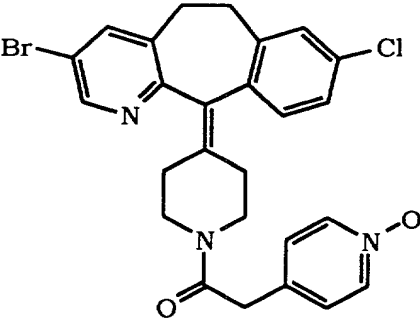
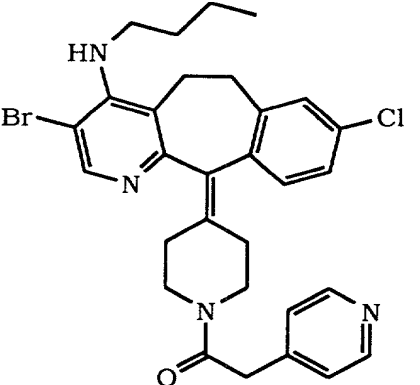
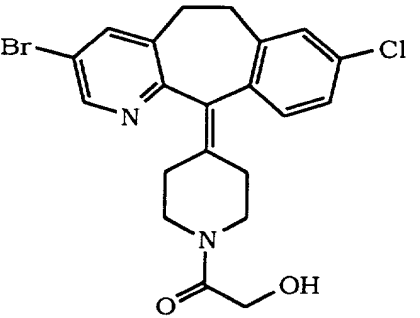
| Starting Compound      | Product Compound     | Analytical Data            |
|------------------------|----------------------|----------------------------|
| Preparative Example 49 | <p>Example 400-A</p> | Mass Spec:<br>$MH^+ = 458$ |

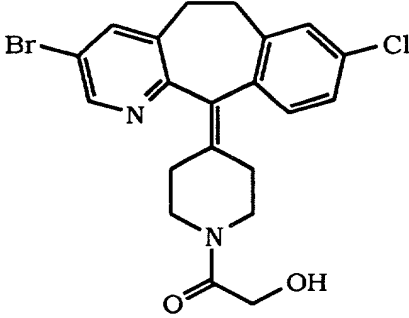
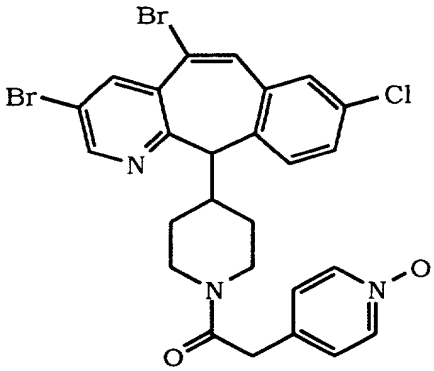
|                                    |   |   |
|------------------------------------|---|---|
| <p>Preparative<br/>Example 53C</p> |  <p>Example 400-B (5.203)</p>   | <p>Mass Spec.:<br/>MH<sup>+</sup> = 528.2</p> |
| <p>Preparative<br/>Example 53C</p> |  <p>Example 400-C (5.200)</p>  | <p>Mass Spec.:<br/>MH<sup>+</sup> = 524.2</p> |
| <p>Preparative<br/>Example 53C</p> |  <p>Example 400-D (5.217)</p> | <p>Mass Spec.:<br/>MH<sup>+</sup> = 524.1</p> |



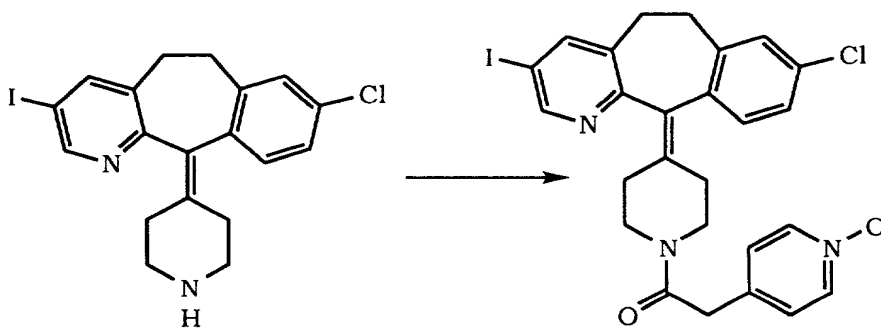
|                                    |   |  |
|------------------------------------|---|--|
| <p>Preparative<br/>Example 51A</p> |  <p>Example 400-E (5.208)</p>   | <p>Mass Spec.:<br/><math>MH^+ = 512.1</math></p> |
| <p>Preparative<br/>Example 51A</p> |  <p>Example 400-F (5.201)</p>  | <p>Mass Spec.:<br/><math>MH^+ = 528</math></p>   |
| <p>Preparative<br/>Example 53C</p> |  <p>Example 400-G (5.204)</p> | <p>Mass Spec.:<br/><math>MH^+ = 508.0</math></p> |

|                                    |   |   |
|------------------------------------|---|---|
| <p>Preparative<br/>Example 49</p>  |  <p>Example 400-H (5.220)</p>   | <p>Mass Spec.:<br/>MH<sup>+</sup> = 530.2</p> |
| <p>Preparative<br/>Example 51A</p> |  <p>Example 400-J (5.212)</p>  | <p>Mass Spec.:<br/>MH<sup>+</sup> = 532.3</p> |
| <p>Preparative<br/>Example 49</p>  |  <p>Example 400-K (5.218)</p> | <p>Mass Spec.:<br/>MH<sup>+</sup> = 530.2</p> |

|   |   |   |
|---|---|---|
| <p>Preparative<br/>Example 49</p>             |  <p>Example 400-L (5.206)</p> | <p>Mass Spec.:<br/>MH<sup>+</sup> = 526</p>   |
| <p>Preparative<br/>Example 56,<br/>Step C</p> |  <p>Example 400-M</p>        | <p>Mass Spec.:<br/>MH<sup>+</sup> = 581</p>   |
| <p>Preparative<br/>Example 49</p>             |  <p>Example 400-N</p>       | <p>Mass Spec.:<br/>MH<sup>+</sup> = 449.2</p> |

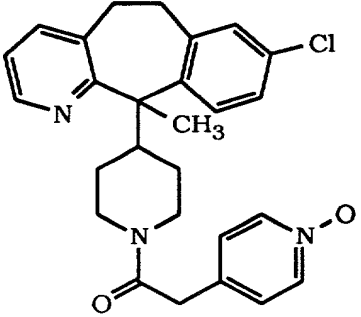
|                                    |  |  |
|------------------------------------|--|--|
| <p>Preparative<br/>Example 51A</p> |  <p>Example 400-P</p>  | <p>m.p. = 62.8°-<br/>63.5°C<br/>Mass Spec.:<br/>MH<sup>+</sup> = 451</p> |
| <p>Preparative<br/>Example 53B</p> |  <p>Example 400-Q</p> | <p>Mass Spec.:<br/>MH<sup>+</sup> = 602</p>                              |

### EXAMPLE 401

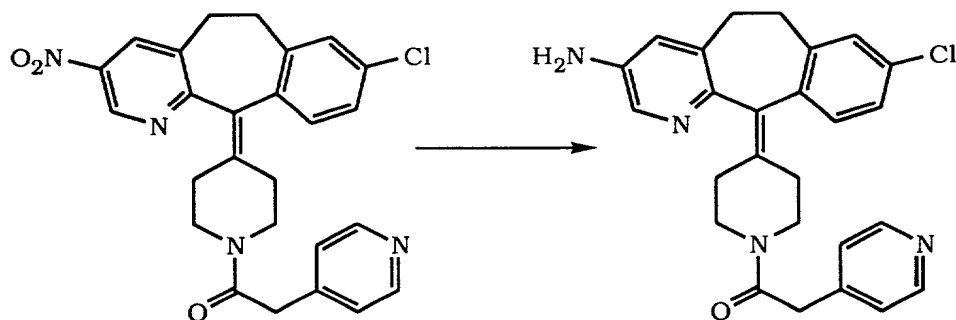


- 5 The product of Preparative Example 48, Step B, is reacted with 4-pyridyl acetic acid N-oxide via essentially the same procedure as described in Example 227 to give the product compound (5.209).  
Mass Spec.: MH<sup>+</sup> = 572

- 10 Using the appropriate carboxylic acid and the starting compound indicated, the following compounds were prepared via substantially the same procedure as described for Example 401:

| Starting Compound      | Product Compound  | Analytical Data                     |
|------------------------|---|-------------------------------------|
| Preparative Example 50 |  <p>Example 401-A</p> | Mass Spec:<br>MH <sup>+</sup> = 462 |

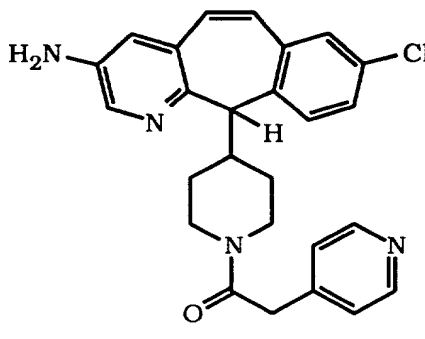
#### EXAMPLE 402



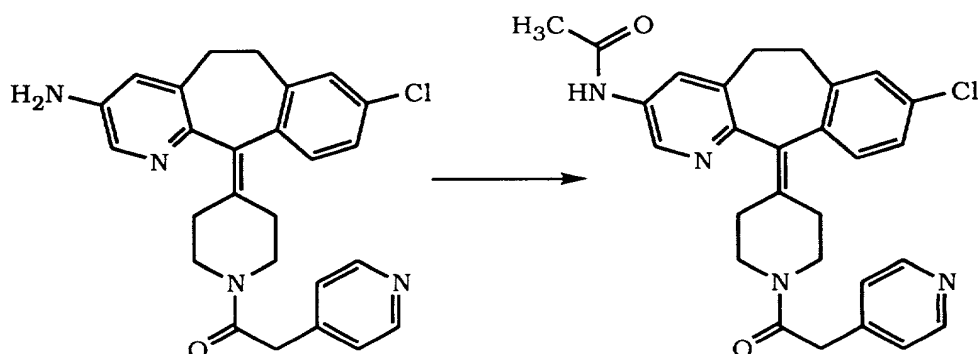
5

The product of Example 358, Step B, is reduced via essentially the same procedure as described in Step B of Preparative Example 47 to give the product compound. mp=133.2-133.4 °C MH<sup>+</sup> 445

Using the starting compound indicated, the following compounds  
10 were prepared via substantially the same procedure as described for Example 402:

| Starting Compound | Product Compound  | Analytical Data                        |
|-------------------|---|--|
| Example 411-B     |  <p>Example 402-A</p> | Mass Spec.:<br>MH <sup>+</sup> = 445.2 |

### EXAMPLE 403

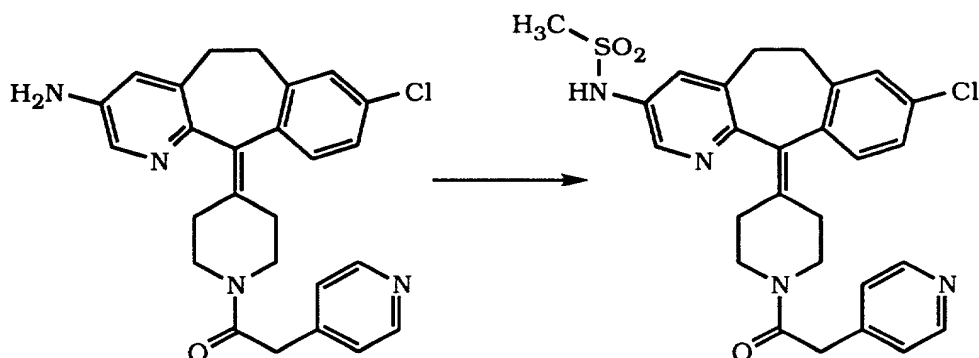


5

Combine 0.3 g (0.67 mmol) of the product of Example 402, 5 mL of pyridine and 0.1 g (1.01 mmol) of acetic anhydride and stir the mixture at room temperature for 2 days. Add another 100  $\mu$ L of acetic anhydride, warm to 60°C and stir for 6h. Neutralize the reaction mixture then basify with 1 N NaOH (aqueous) to pH =10. Extract with CH<sub>2</sub>Cl<sub>2</sub>, dry the extract over MgSO<sub>4</sub> and concentrate to a residue. Purify the residue by HPLC eluting 8% MeOH/CH<sub>2</sub>Cl<sub>2</sub> + concentrated NH<sub>4</sub>OH (aqueous) to give 0.22 g of the product compound. Mass Spec.: MH<sup>+</sup> = 487

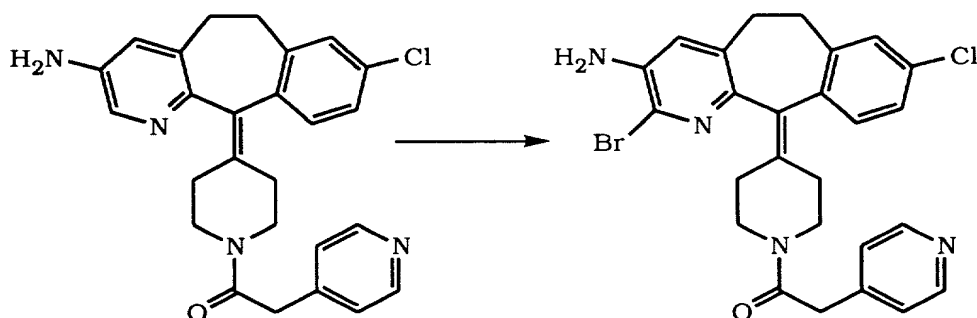
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EXAMPLE 404



5 The product of Example 402 is reacted with methanesulfonyl chloride via substantially the same procedure as described for Example 403 to give the 0.32 g of the product compound. Mass Spec.:  $\text{MH}^+ = 523$

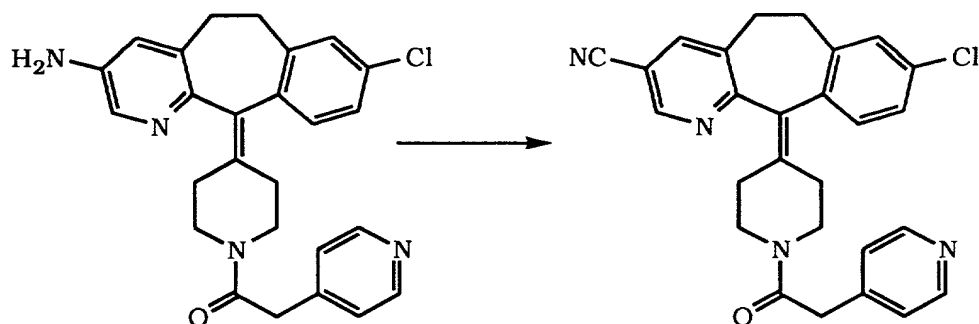
EXAMPLE 405



10

Combine 1.5 g (3.37 mmol) of the product of Example 402 and 10 mL of AcOH, then add 3.37 mL of a solution of bromine in AcOH and stir the mixture at room temperature overnight. Basify the mixture with 1N NaOH (aqueous) to basic pH, then extract with EtOAc. Concentrate the  
15 extract to a residue and chromatograph (silica gel, 90% EtOAc/hexane, then 5% Et<sub>3</sub>N/EtOAc) to give the product compound. Mass Spec.:  $\text{MH}^+ = 525$ .

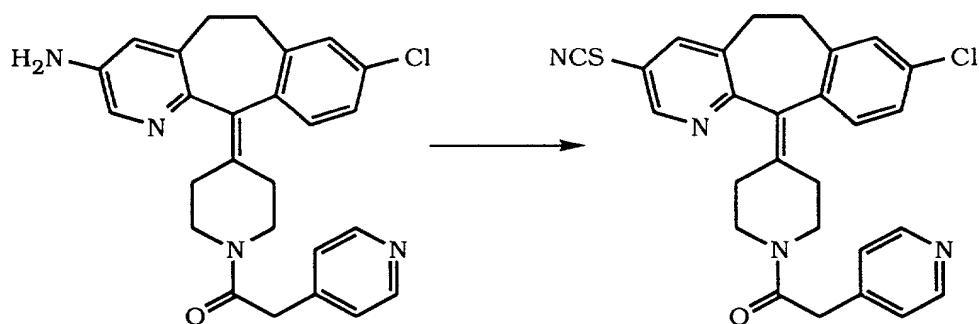
EXAMPLE 406



Combine 0.5 g (1.12 mmol) of the product of Example 402 and 10  
 5 mL of acetone, add 230  $\mu$ L of conc. HCl (aqueous) and 4 mL of water, and  
 cool to  $-10^{\circ}\text{C}$ . Add a solution of 0.085 g  $\text{NaNO}_2$  in 4 mL of water, stir for  
 15 min., then add the reaction mixture to a solution of CuCN [freshly  
 prepared by adding 0.336 g (1.34 mmol) of  $\text{CuSO}_4$  in 2 mL of water to  
 $\text{H}_2\text{O}$  a solution of 0.365 g (5.6 mmol) of KCN in 2 mL of  $\text{H}_2\text{O}$ ]. Heat the  
 10 mixture to  $60^{\circ}\text{C}$ - $70^{\circ}\text{C}$ , then at  $70^{\circ}\text{C}$ - $80^{\circ}\text{C}$  to remove acetone. Cool the  
 mixture and dilute with  $\text{H}_2\text{O}$ , then exhaustively extracted with  $\text{CH}_2\text{Cl}_2$ .  
 Concentrate the extracts to a residue then purify by HPLC using 3 %  
 methanolic ammonia in  $\text{CH}_2\text{Cl}_2$  to give 0.25 g (50% yield) of the product  
 compound. Mass Spec.:  $\text{MH}^+ = 455$ .

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EXAMPLE 407

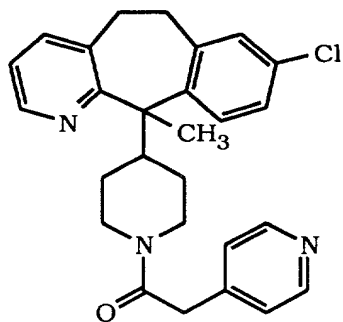


Combine 0.55 g (1.25 mmol) of the product of Example 402 and 50  
 20 mL of dilute  $\text{H}_2\text{SO}_4$  at room temperature. Cool the mixture to  $-10^{\circ}\text{C}$ , add  
 a solution of 0.092 g of  $\text{NaNO}_2$  in 5 mL of water was added and stir for 15  
 min. Slowly add a solution of 0.46 g (4.7 mmol) of KSCN and 0.3 g (2.49  
 mmol) of CuSCN in 15 mL of water over a period of 0.5 hours. Stir for 0.5  
 hour then heat at reflux for 15 min. Cool the mixture and adjust the pH to  
 25  $\sim 7$ , then extract with  $\text{CH}_2\text{Cl}_2$ . Concentrate the extracts to a residue and



chromatograph (silica gel, 3% MeOH/CH<sub>2</sub>Cl<sub>2</sub> + NH<sub>4</sub>OH) to give the product compound. Mass Spec.: MH<sup>+</sup> = 487

**EXAMPLE 410**



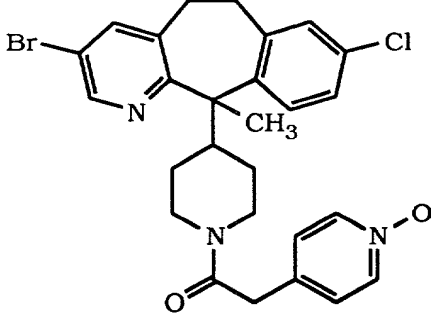
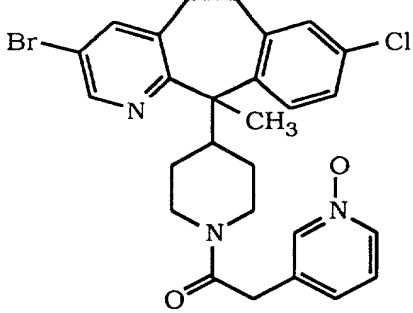
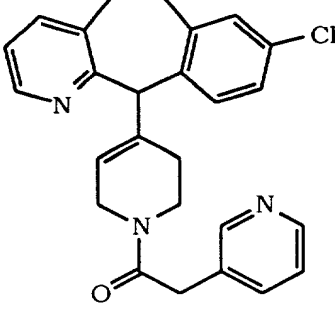
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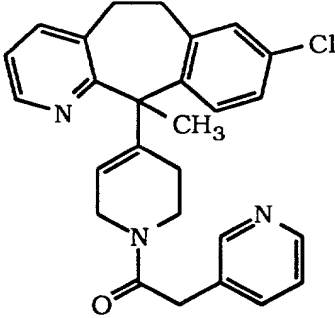
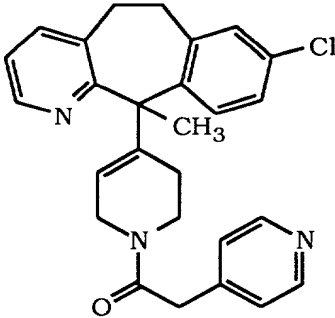
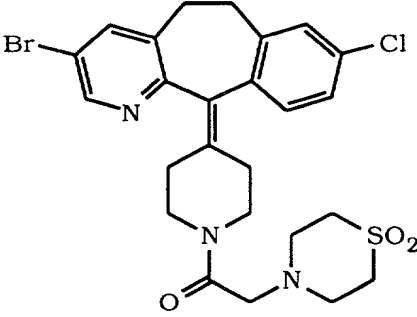
The product of Preparative Example 50 was reacted with 4-pyridylacetic acid via substantially the same procedure as described for Example 180 to give the product compound. Mass Spec.: MH<sup>+</sup> = 446

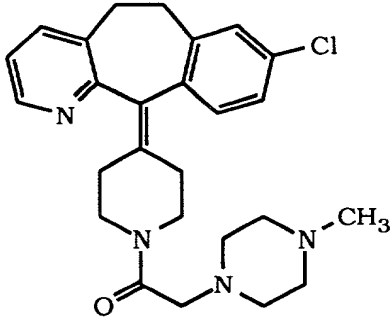
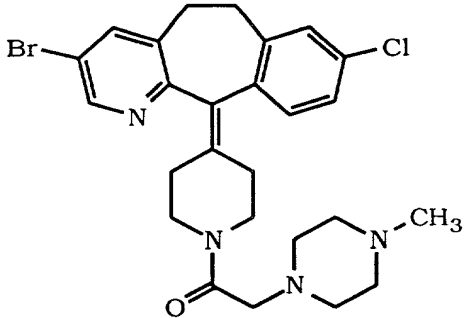
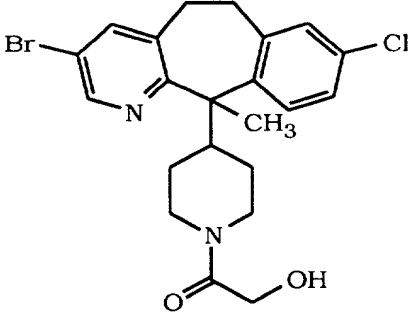
10

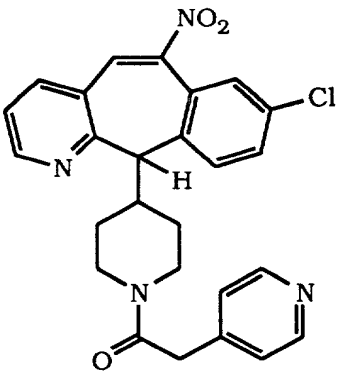
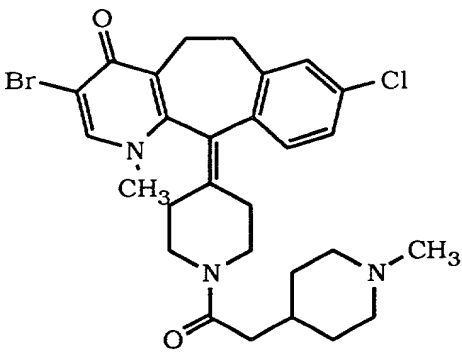
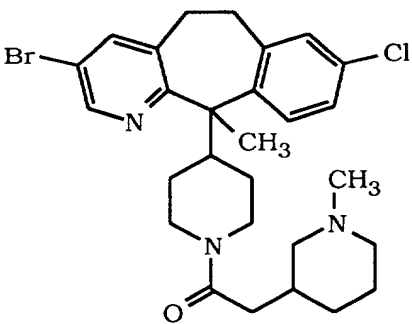
Using the appropriate carboxylic acid and the starting compound indicated, the following compounds were prepared via substantially the same procedure as described for Example 410:

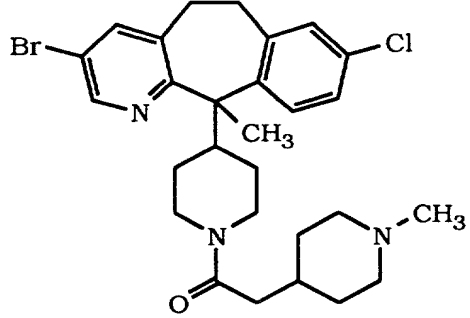
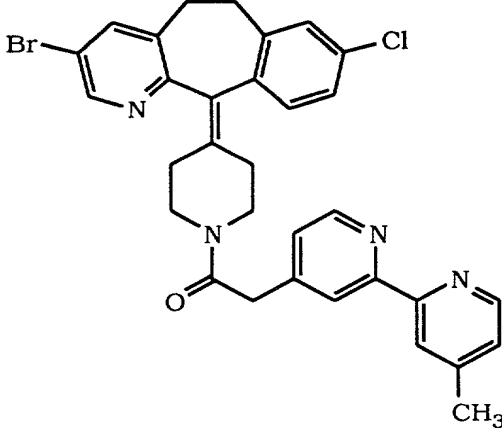
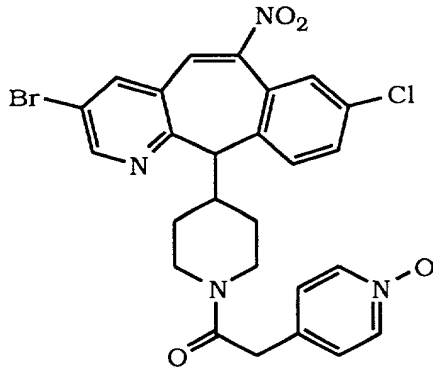
| Starting Compound       | Product Compound     | Analytical Data                      |
|-------------------------|----------------------|--------------------------------------|
| Preparative Example 49A | <p>Example 410-A</p> | Mass Spec.:<br>MH <sup>+</sup> = 526 |

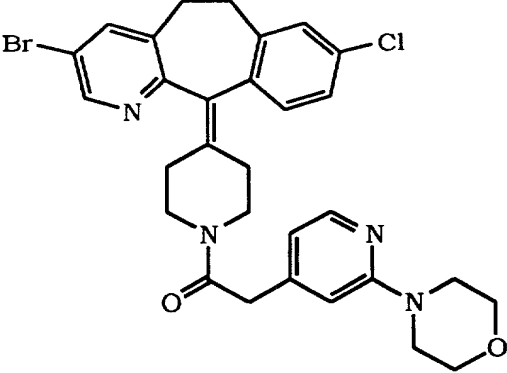
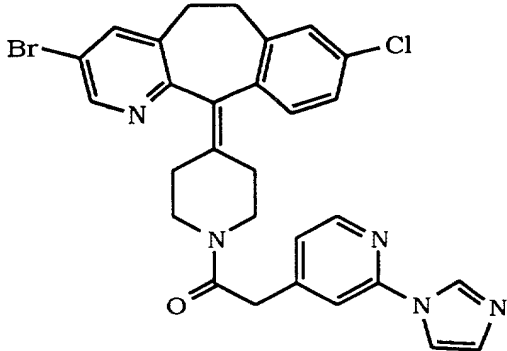
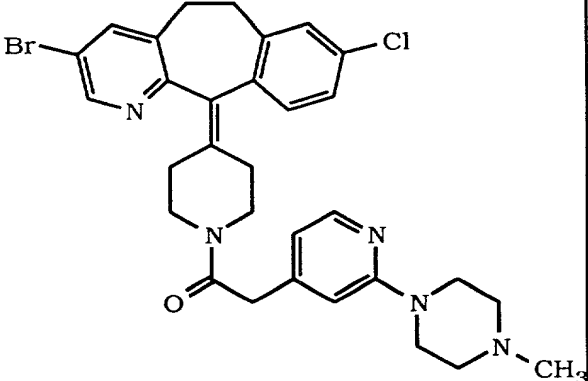
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| <p>Preparative<br/>Example 49A</p> |  <p>Example 410-B</p>   | <p>Mass Spec.:<br/>MH<sup>+</sup> = 542</p>                             |
| <p>Preparative<br/>Example 49A</p> |  <p>Example 410-C</p>  | <p>Mass Spec.:<br/>MH<sup>+</sup> = 542</p>                             |
| <p>Preparative<br/>Example 52</p>  |  <p>Example 410-D</p> | <p>m.p. = 67°-<br/>69°C</p> <p>Mass Spec.:<br/>MH<sup>+</sup> = 430</p> |

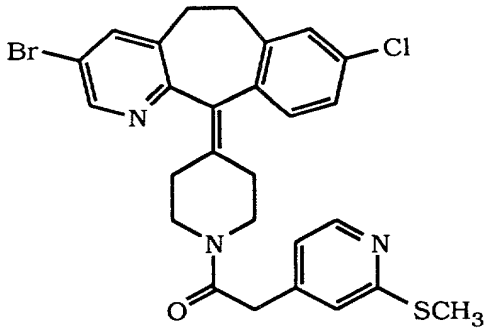
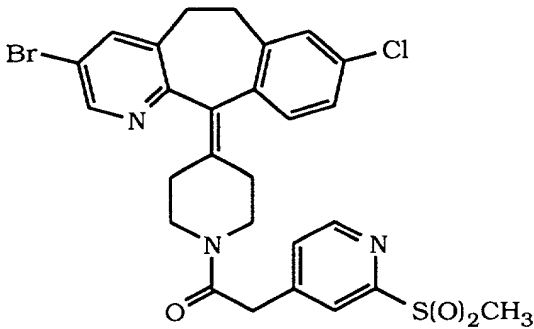
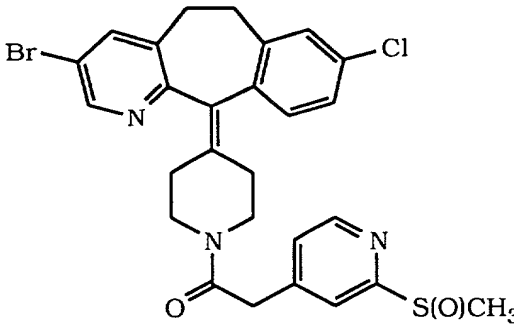
|                                    |   |   |
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| <p>Preparative<br/>Example 52A</p> |  <p>Example 410-E</p>   | <p>m.p. = 77°-<br/>78°C</p> <p>Mass Spec.:<br/>MH<sup>+</sup> = 444</p>   |
| <p>Preparative<br/>Example 52A</p> |  <p>Example 410-F</p>  | <p>m.p. = 78°-<br/>79°C</p> <p>Mass Spec.:<br/>MH<sup>+</sup> = 444</p>   |
| <p>Preparative<br/>Example 49</p>  |  <p>Example 410-G</p> | <p>m.p. = 137°-<br/>138°C</p> <p>Mass Spec.:<br/>MH<sup>+</sup> = 565</p> |

|                                    |   |  |
|------------------------------------|---|--|
| <p>Preparative<br/>Example 1</p>   |  <p>Example 410-H</p>   | <p>Mass Spec.:<br/>MH<sup>+</sup> = 451.2</p>                                |
| <p>Preparative<br/>Example 49</p>  |  <p>Example 410-J</p>  | <p>Mass Spec.:<br/>MH<sup>+</sup> = 531.2</p>                                |
| <p>Preparative<br/>Example 49A</p> |  <p>Example 410-K</p> | <p>m.p. = 108.8°-<br/>109.7°C<br/>Mass Spec.:<br/>MH<sup>+</sup> = 465.4</p> |

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| <p>Preparative<br/>Example 53</p>  |  <p>Example 410-L</p>   | <p>Mass Spec.:<br/>MH<sup>+</sup> = 475.2</p>                              |
| <p>Preparative<br/>Example 57</p>  |  <p>Example 410-M</p>  | <p>m.p. = 151°-<br/>153°C<br/>Mass Spec.:<br/>MH<sup>+</sup> = 560</p>     |
| <p>Preparative<br/>Example 49A</p> |  <p>Example 410-N</p> | <p>m.p. = 164.8°-<br/>165.2°C<br/>Mass Spec.:<br/>MH<sup>+</sup> = 546</p> |

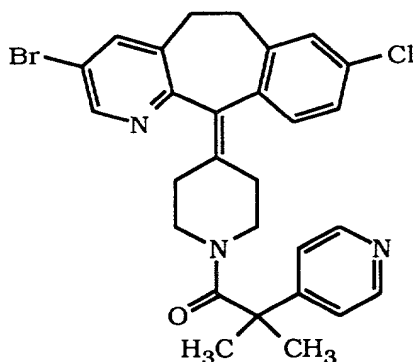
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| <p>Preparative<br/>Example 49A</p> |  <p>Example 410-P</p>   | <p>m.p. = 124.2°-<br/>125°C<br/>Mass Spec.:<br/>MH<sup>+</sup> = 546</p>   |
| <p>Preparative<br/>Example 49</p>  |  <p>Example 410-Q</p>  | <p>m.p. = 102.6°-<br/>103°C<br/>Mass Spec.:<br/>MH<sup>+</sup> = 601.2</p> |
| <p>Preparative<br/>Example 73</p>  |  <p>Example 410-R</p> | <p>Mass Spec.:<br/>MH<sup>+</sup> = 569</p>                                |

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| <p>Preparative<br/>Example 49</p> |  <p>Example 410-S</p>   | <p>m.p. = 97°C<br/>(dec.)<br/>Mass Spec.:<br/>MH<sup>+</sup> = 595</p>   |
| <p>Preparative<br/>Example 49</p> |  <p>Example 410-T</p>  | <p>m.p.= 132.6°C<br/>(dec.)<br/>Mass Spec.:<br/>MH<sup>+</sup> = 576</p> |
| <p>Preparative<br/>Example 49</p> |  <p>Example 410-U</p> | <p>m.p.= 111.2°C<br/>(dec.)<br/>Mass Spec.:<br/>MH<sup>+</sup> = 608</p> |

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|-----------------------------------|---|---|
| <p>Preparative<br/>Example 49</p> |  <p>Example 410-V</p>   | <p>m.p.= 85.1°C<br/>(dec.)<br/>Mass Spec.:<br/>MH<sup>+</sup> = 556</p>   |
| <p>Preparative<br/>Example 49</p> |  <p>Example 410-W</p>  | <p>m.p.= 114°C<br/>(dec.)<br/>Mass Spec.:<br/>MH<sup>+</sup> = 588</p>    |
| <p>Preparative<br/>Example 49</p> |  <p>Example 410-X</p> | <p>m.p.= 122.5°-<br/>126.0°C<br/>Mass Spec.:<br/>MH<sup>+</sup> = 572</p> |



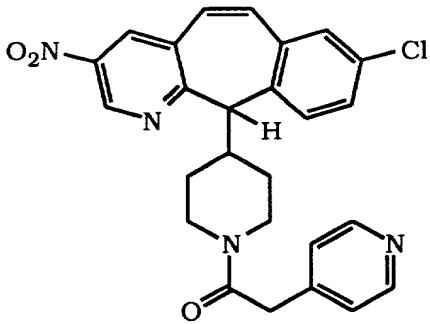
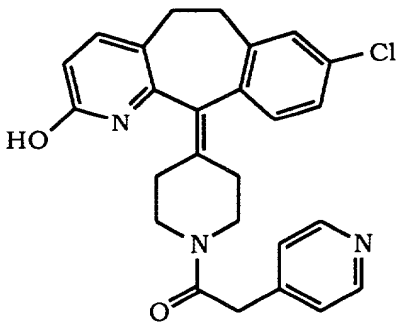
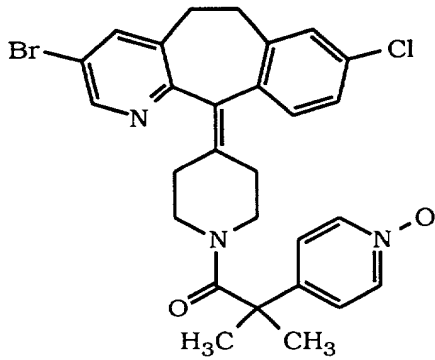
EXAMPLE 411

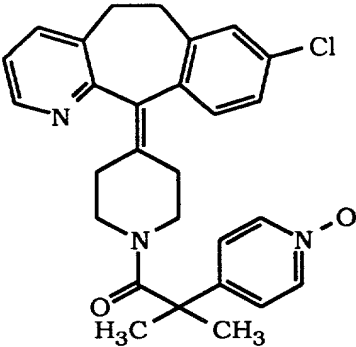
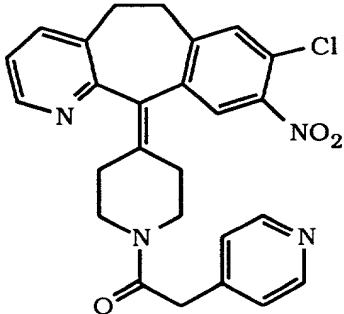
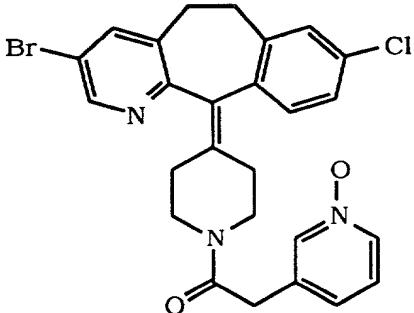


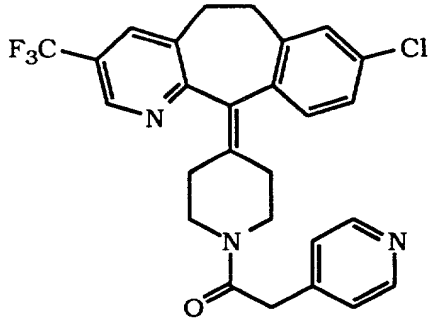
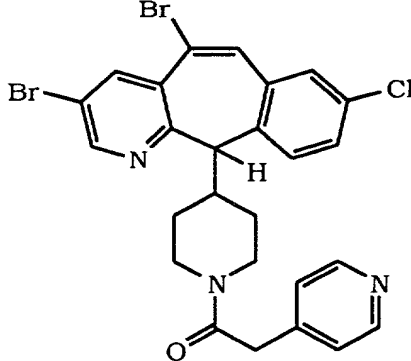
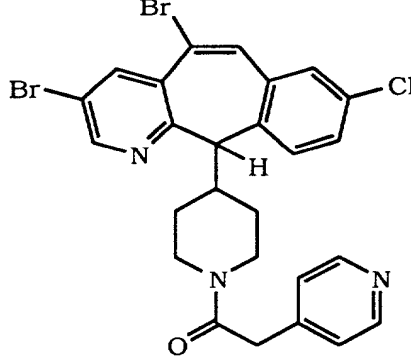
The product of Preparative Example 49 was reacted with 2-methyl-  
 5 2-(4-pyridyl)propanoic acid via substantially the same procedure as  
 described for Example 180 to give the product compound. Mass Spec.:  
 MH<sup>+</sup> = 538

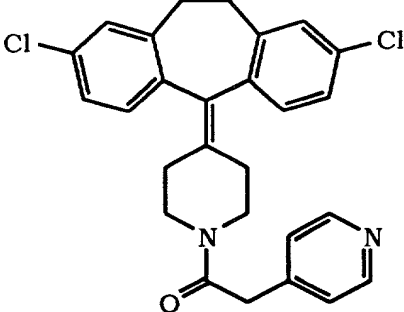
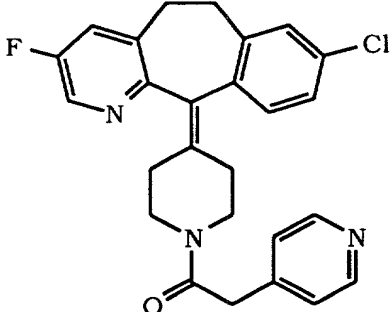
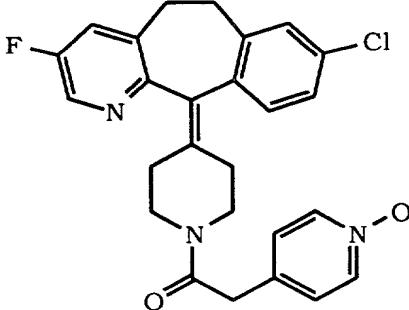
Using the appropriate carboxylic acid (or carboxylate salt, e.g.  
 lithium carboxylate) and the starting compound indicated, the following  
 10 compounds were prepared via substantially the same procedure as  
 described for Example 410:

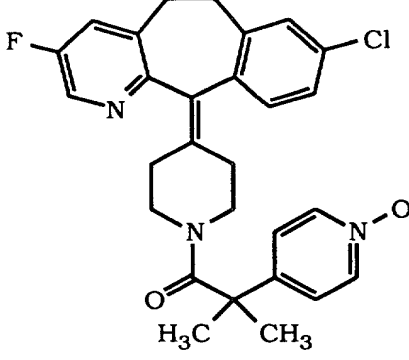
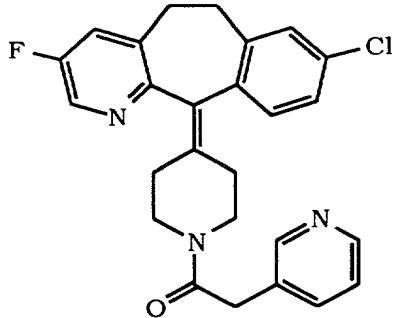
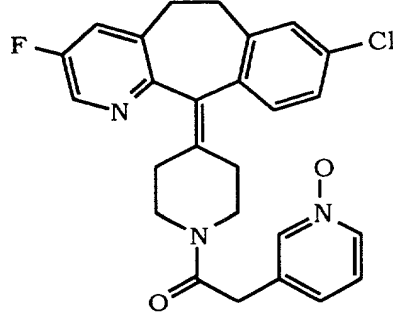
| Starting Compound      | Product Compound     | Analytical Data                      |
|------------------------|----------------------|--------------------------------------|
| Preparative Example 49 | <p>Example 411-A</p> | Mass Spec.:<br>MH <sup>+</sup> = 554 |

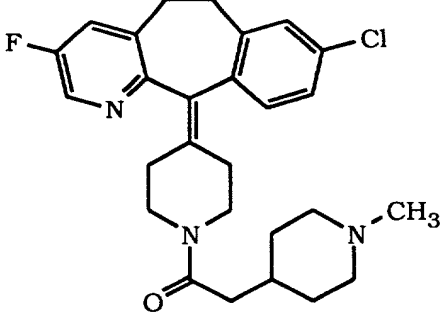
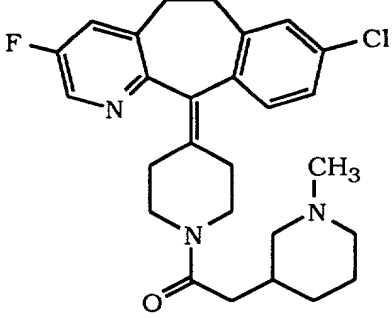
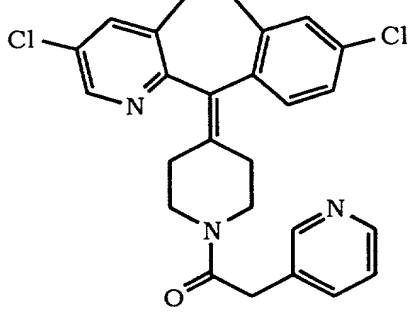
|  |   |  |
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| <p>Preparative<br/>Example<br/>53A</p> |  <p>Example 411-B</p>   | <p>Mass Spec.:<br/>MH<sup>+</sup> = 475.2</p>                              |
| <p>Preparative<br/>Example 55</p>      |  <p>Example 411-C</p>  | <p>m.p. = 155.2°-<br/>158.9°C<br/>Mass Spec.:<br/>MH<sup>+</sup> = 446</p> |
| <p>Preparative<br/>Example 49</p>      |  <p>Example 411-D</p> | <p>Mass Spec.:<br/>MH<sup>+</sup> = 554</p>                                |

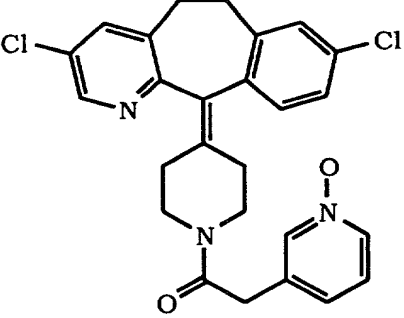
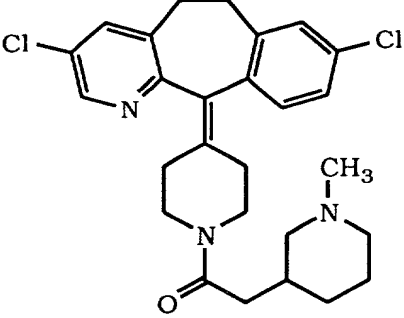
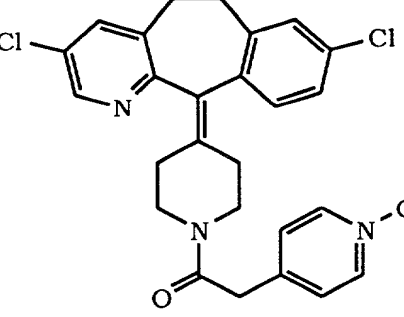
|                                   |   |   |
|-----------------------------------|---|---|
| <p>Preparative<br/>Example 1</p>  |  <p>Example 411-E</p>   | <p>Mass Spec.:<br/>MH<sup>+</sup> = 474</p>   |
| <p>Preparative<br/>Example 72</p> |  <p>Example 411-F</p>  | <p>Mass Spec.:<br/>MH<sup>+</sup> = 475</p>   |
| <p>Preparative<br/>Example 49</p> |  <p>Example 411-G</p> | <p>Mass Spec.:<br/>MH<sup>+</sup> = 526.1</p> |

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| <p>Preparative<br/>Example 71</p>  |  <p>Example 411-H</p>   | <p>Mass Spec.:<br/>MH<sup>+</sup> = 498</p> |
| <p>Preparative<br/>Example 53B</p> |  <p>Example 411-J</p>  | <p>Mass Spec.:<br/>MH<sup>+</sup> = 586</p> |
| <p>Preparative<br/>Example 53B</p> |  <p>Example 411-K</p> | <p>Mass Spec.:<br/>MH<sup>+</sup> = 581</p> |

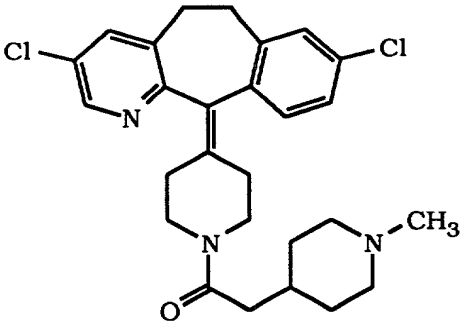
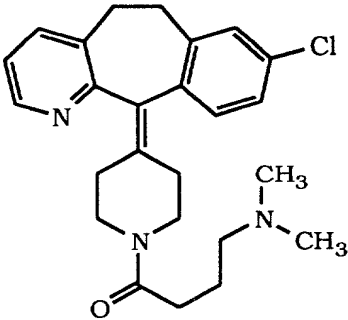
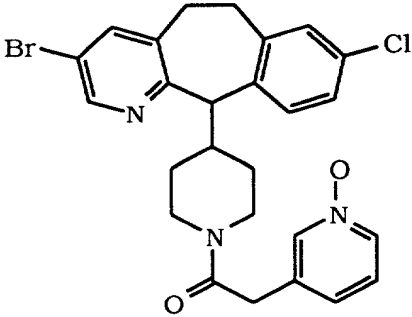
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| <p>Preparative<br/>Example 59</p> |  <p>Example 411-L</p>   | <p>m.p. = 97°-<br/>98°C<br/>Mass Spec.:<br/>(FAB) MH<sup>+</sup> =<br/>463.1</p> |
| <p>Preparative<br/>Example 60</p> |  <p>Example 411-M</p>   | <p>Mass Spec.:<br/>MH<sup>+</sup> = 448</p>                                      |
| <p>Preparative<br/>Example 60</p> |  <p>Example 411-N</p> | <p>Mass Spec.:<br/>MH<sup>+</sup> = 464</p>                                      |

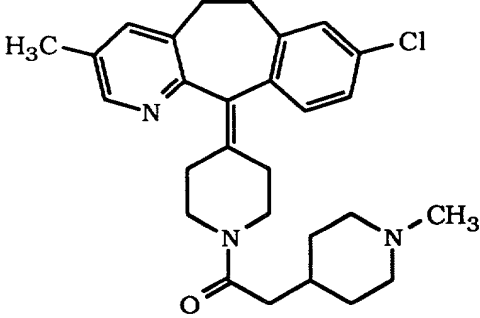
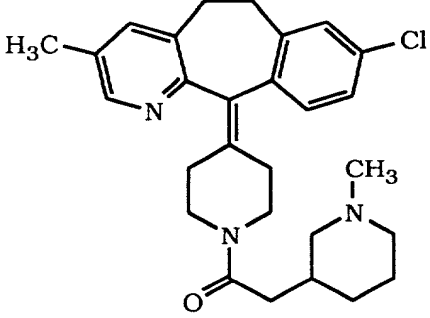
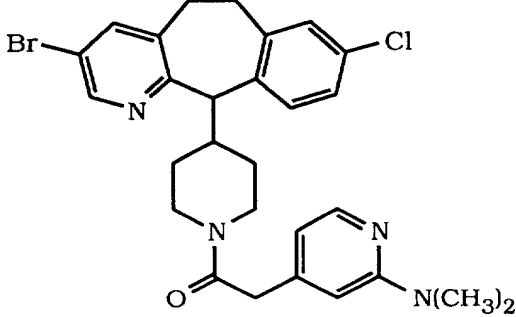
|                                   |   |   |
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| <p>Preparative<br/>Example 60</p> |  <p>Example 411-O</p>   | <p>Mass Spec.:<br/>MH<sup>+</sup> = 492</p> |
| <p>Preparative<br/>Example 60</p> |  <p>Example 411-P</p>  | <p>Mass Spec.:<br/>MH<sup>+</sup> = 448</p> |
| <p>Preparative<br/>Example 60</p> |  <p>Example 411-Q</p> | <p>Mass Spec.:<br/>MH<sup>+</sup> = 464</p> |

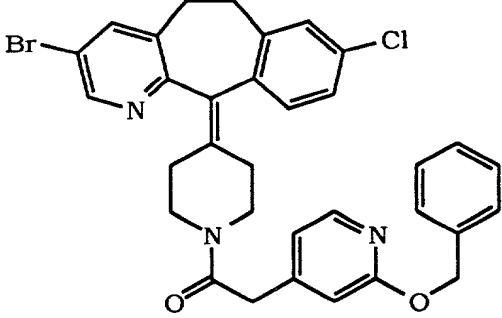
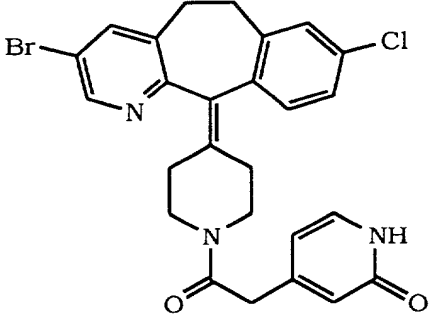
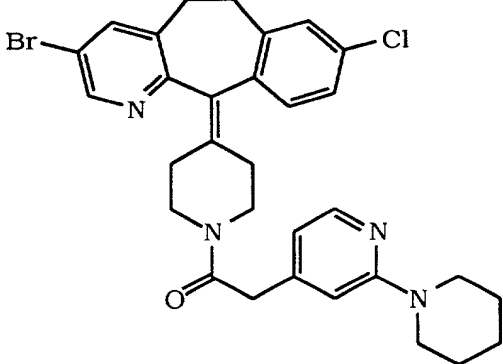
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| <p>Preparative<br/>Example 60</p>      |  <p>Example 411-R</p>   | <p>Mass Spec.:<br/>MH<sup>+</sup> = 469</p> |
| <p>Preparative<br/>Example 60</p>      |  <p>Example 411-S</p>  | <p>Mass Spec.:<br/>MH<sup>+</sup> = 469</p> |
| <p>Preparative<br/>Example<br/>60A</p> |  <p>Example 411-T</p> | <p>Mass Spec.:<br/>MH<sup>+</sup> = 465</p> |

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|--|---|---|
| <p>Preparative<br/>Example<br/>60A</p> |  <p>Example 411-U</p>   | <p>Mass Spec.:<br/>MH<sup>+</sup> = 481</p> |
| <p>Preparative<br/>Example<br/>60A</p> |  <p>Example 411-V</p>  | <p>Mass Spec.:<br/>MH<sup>+</sup> = 485</p> |
| <p>Preparative<br/>Example<br/>60A</p> |  <p>Example 411-W</p> | <p>Mass Spec.:<br/>MH<sup>+</sup> = 481</p> |

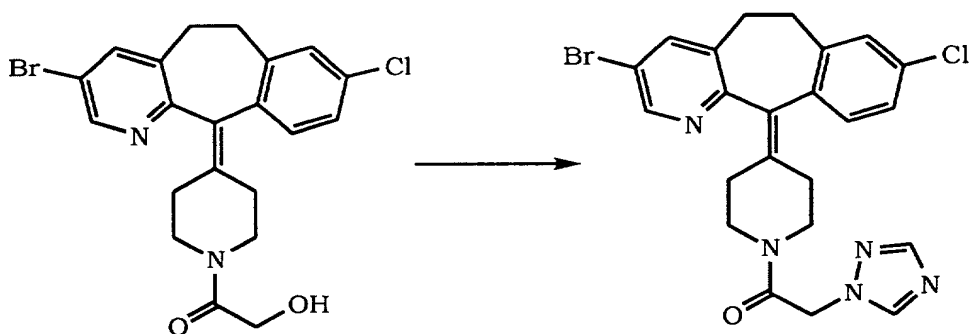
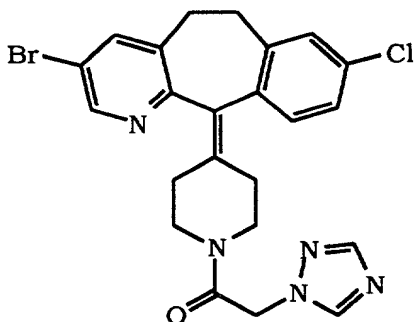


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|---|--|--|
| <p>Preparative<br/>Example<br/>60A</p>      |  <p>Example 411-X</p>    | <p>Mass Spec.:<br/>MH<sup>+</sup> = 485</p>                              |
| <p>Preparative<br/>Example 1<br/>Step G</p> |  <p>Example 411-Z</p>   | <p>-----</p>   |
| <p>Preparative<br/>Example<br/>51A</p>      |  <p>Example 411-AA</p> | <p>m.p. = 125°-<br/>125.4°C<br/>Mass Spec.:<br/>MH<sup>+</sup> = 528</p> |

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| <p>Preparative<br/>Example 3<br/>Step E</p> |  <p>Example 411-BB</p>   | <p>m.p. = 186.6°-<br/>187°C<br/>Mass Spec.:<br/>MH<sup>+</sup> = 464</p> |
| <p>Preparative<br/>Example 3<br/>Step E</p> |  <p>Example 411-CC</p>  | <p>Mass Spec.:<br/>MH<sup>+</sup> = 464</p>                              |
| <p>Preparative<br/>Example<br/>51A</p>      |  <p>Example 411-DD</p> | <p>-----</p>   |

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| <p>Preparative<br/>Example 49</p> |  <p>Example 411-EE</p>   | <p>m.p. = 83°-<br/>86°C<br/>Mass Spec.:<br/>MH<sup>+</sup> = 616</p>   |
| <p>Preparative<br/>Example 49</p> |  <p>Example 411-FF</p>  | <p>m.p. = 167°-<br/>171°C<br/>Mass Spec.:<br/>MH<sup>+</sup> = 526</p> |
| <p>Preparative<br/>Example 49</p> |  <p>Example 411-GG</p> | <p>m.p. = 134°-<br/>140°C<br/>Mass Spec.:<br/>MH<sup>+</sup> = 593</p> |

EXAMPLE 412

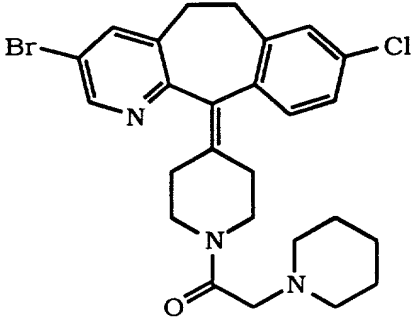
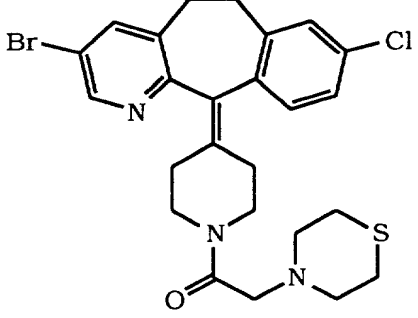
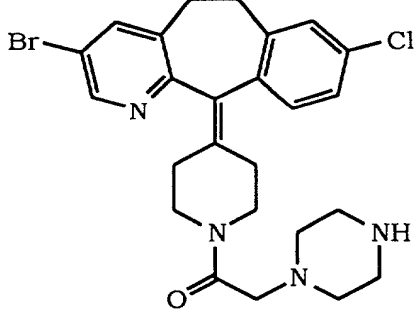


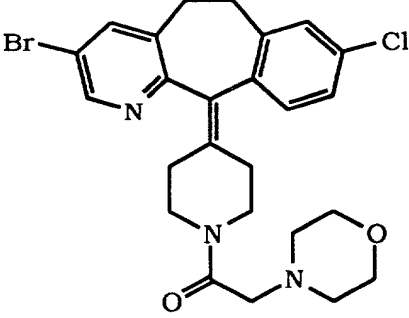
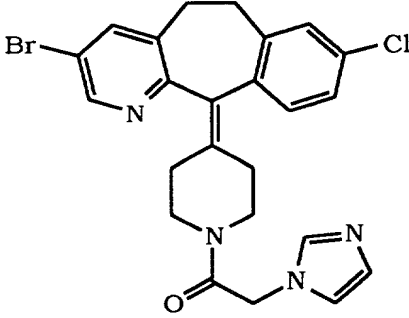
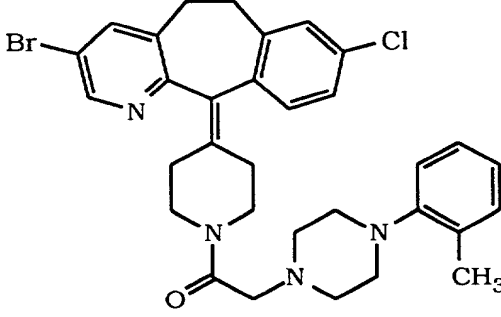
5

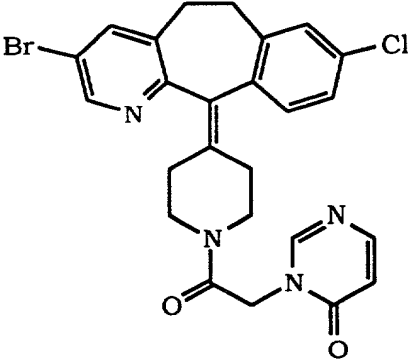
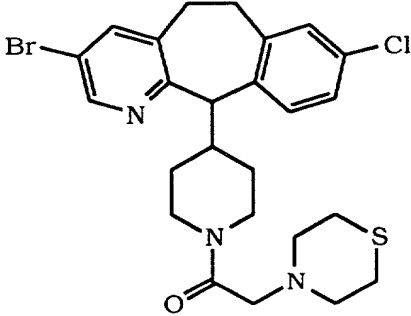
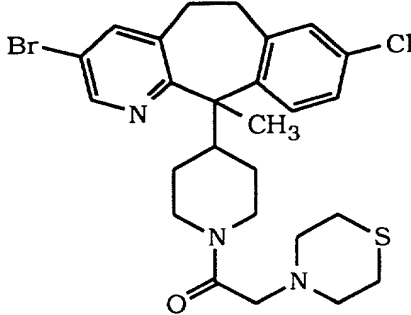
Combine 50 mg (0.11 mmol) of the compound of Example 400-N, and 1.5 mL of  $\text{SOCl}_2$  and stir at room temperature overnight. Concentrate *in vacuo* to a residue, add 2.0 mL of DMF to the residue, then add 20 mg (0.2 mmol) of 1,2,4-triazole sodium salt and heat to  $100^\circ\text{C}$  overnight. Cool the mixture, concentrate *in vacuo* to remove most of the solvent, wash with water (3 times), then dry the residue over  $\text{Na}_2\text{SO}_4$ . Concentrate *in vacuo* to a residue and chromatograph (silica gel, 75% (10%  $\text{NH}_4\text{OH}$  in MeOH) in  $\text{CH}_2\text{Cl}_2$ ) to give 26 mg of the product compound. Mass Spec.:  $\text{MH}^+ = 498$

15

Using the appropriate starting compound and substantially the same procedure as described for Example 412, but substituting the amine nucleophile indicated in place of the 1,2,4-triazole sodium salt, the following compounds were prepared:

| Amine Nucleophile   | Product Compound  | Analytical Data                               |
|---|---|---|
| <p>piperidine</p> <p>(solvent is CH<sub>2</sub>Cl<sub>2</sub> instead of DMF)</p>     |  <p>Example 412-A</p>   | <p>Mass Spec.:<br/>MH<sup>+</sup> = 514.2</p> |
| <p>thiomorpholine</p> <p>(solvent is CH<sub>2</sub>Cl<sub>2</sub> instead of DMF)</p> |  <p>Example 412-B</p>  | <p>Mass Spec.:<br/>MH<sup>+</sup> = 532.1</p> |
| <p>piperazine</p> <p>(solvent is CH<sub>2</sub>Cl<sub>2</sub> instead of DMF)</p>     |  <p>Example 412-C</p> | <p>Mass Spec.:<br/>MH<sup>+</sup> = 515</p>   |

|   |   |   |
|---|---|---|
| <p>morpholine</p> <p>(solvent is<br/>CH<sub>2</sub>Cl<sub>2</sub> instead<br/>of DMF)</p>                               |  <p>Example 412-D</p>   | <p>Mass Spec.:<br/>MH<sup>+</sup> = 516.1</p> |
| <p>imidazole</p> <p>(solvent is<br/>CH<sub>2</sub>Cl<sub>2</sub> instead<br/>of DMF)</p>                                |  <p>Example 412-E</p>  | <p>Mass Spec.:<br/>MH<sup>+</sup> = 497.2</p> |
| <p>N-(2-methyl-<br/>phenyl)-<br/>piperazine</p> <p>(solvent is<br/>CH<sub>2</sub>Cl<sub>2</sub> instead<br/>of DMF)</p> |  <p>Example 412-F</p> | <p>Mass Spec.:<br/>MH<sup>+</sup> = 605.1</p> |

|                              |   |  |
|------------------------------|---|--|
| <p>4(3H)-<br/>pyrimidone</p> |  <p>Example 412-G</p>   | <p>Mass Spec.:<br/>MH<sup>+</sup> = 525.1</p>                              |
| <p>thiomorpholine</p>        |  <p>Example 412-H</p>  | <p>m.p. = 105°-<br/>105.6°C<br/>Mass Spec.:<br/>MH<sup>+</sup> = 536</p>   |
| <p>thiomorpholine</p>        |  <p>Example 412-J</p> | <p>m.p. = 102.5°-<br/>102.9°C<br/>Mass Spec.:<br/>MH<sup>+</sup> = 550</p> |

CN1CCCC1CC(=O)N2CCCC2C(=C3C4=CC=C(C=C4)C(=C5C(=CC=C5)N=C(C=C5)C(=C6C(=CC=C6)Br)C(=C6)Cl)C3)C2

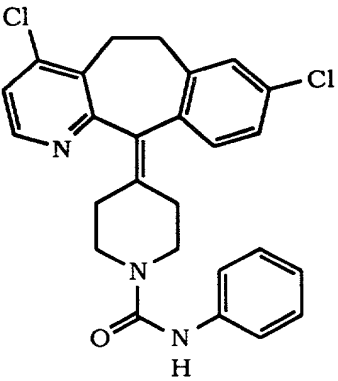
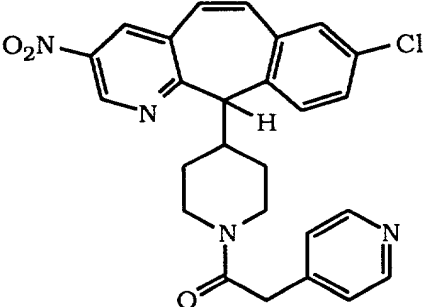
15

O=C1CN(C1)C2=CC=CC=C2C3=C4C(=C(C=C3)C=C(C=C4)Cl)C5=CC=C(C=C5)N=C6C=CC(=C6)BrCl

15                    Combine 84 mg of the product from Preparative Example 46 , 5 mL of pyridine and 0.04 mL of phenylisocyanate and stir at 25°C for 48 hours. Concentrate *in vacuo* to a residue, dilute with CH<sub>2</sub>Cl<sub>2</sub> and wash with saturated NaHCO<sub>3</sub> (aqueous). Dry over MgSO<sub>4</sub>, concentrate to s residue  
20 and chromatograph (silica gel, 50-70% hexane/EtOAc) to give 14 mg (13% yield) of the product compound. m.p. = 125.6°C (dec); Mass Spec.: MH<sup>+</sup> = 544

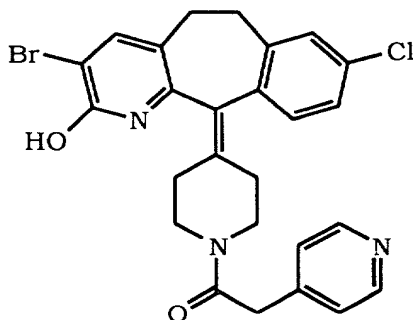


Using the starting compound indicated, the following compounds were prepared via substantially the same procedure as described for Example 414:

| Starting Compound       | Product Compound  | Analytical Data  |
|-------------------------|---|--|
| Preparative Example 28  |  <p>Example 414-A</p>    | <p>m.p. = 131.8°C (dec.)</p> <p>Mass Spec.:<br/>MH<sup>+</sup> = 464</p> |
| Preparative Example 53A |  <p>Example 414-B</p> | <p>Mass Spec.:<br/>MH<sup>+</sup> = 475.2</p>                            |

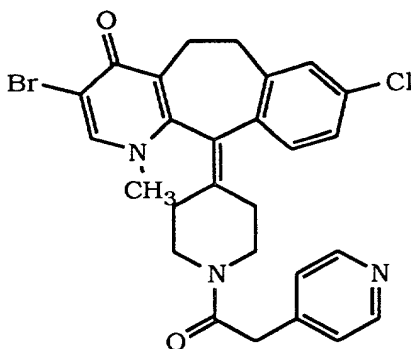
5

#### EXAMPLE 415



- Combine 0.64 g of the product from Example 411-C and 16 mL of glacial HOAc, and add 15 mL of a 0.54 M solution of bromine in HOAc at 25°C under N<sub>2</sub>. After 10 minutes, pour the mixture into water, filter to collect the resulting solid, and wash with water. Dry the solid under vacuum, then chromatograph (silica gel, 6-15% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to give 0.26 grams (35% yield) of the product compound. m.p. = 150.0 °C (dec), Mass Spec.: MH<sup>+</sup> = 526

EXAMPLE 416

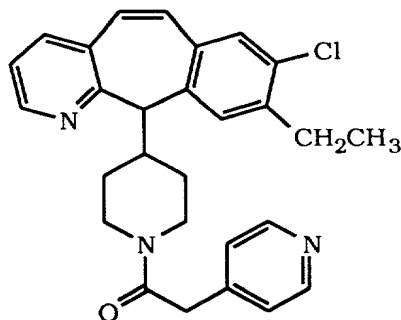


10

- Combine 0.33 g of the product from Preparative Example 57, 2 mL of anhydrous CH<sub>2</sub>Cl<sub>2</sub>, and 10 mL of a mixture of 7.20 g of 4-pyridylacetic acid hydrochloride, 1.61 mL of methanesulfonylchloride, 27 mL of Et<sub>3</sub>N and 60 mL of CH<sub>2</sub>Cl<sub>2</sub>, and stir at 25 °C for 48 hours. Dilute the mixture with CH<sub>2</sub>Cl<sub>2</sub>, wash with saturated NaHCO<sub>3</sub> (aqueous), then with brine. Dry over MgSO<sub>4</sub>, concentrate to a residue and chromatograph (silica gel, 5% MeOH/CH<sub>2</sub>Cl<sub>2</sub> + NH<sub>4</sub>OH) to give 0.23 g (55% yield) of the product compound. m.p. = 142 °C (dec); Mass Spec.: MH<sup>+</sup> = 540

20

EXAMPLE 417

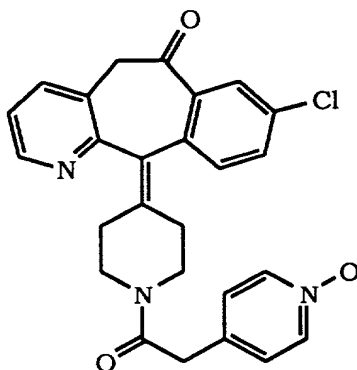


React the product from Preparative Example 35 with 4-pyridylacetic acid via substantially the same procedure as described for Example 266 to give the product compound. Mass Spec.:  $MH^+ = 458$

- 5 Using the appropriate carboxylic acid and the starting compound indicated, the following compounds were prepared via substantially the same procedure as described for Example 417:

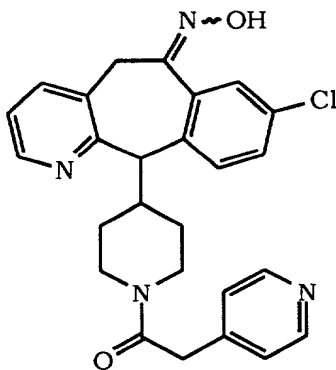
| Starting Compound       | Product Compound     | Analytical Data             |
|-------------------------|----------------------|-----------------------------|
| Preparative Example 37B | <p>Example 417-A</p> | Mass Spec.:<br>$MH^+ = 444$ |
| Preparative Example 58  | <p>Example 417-B</p> | Mass Spec.:<br>$MH^+ = 522$ |

EXAMPLE 418



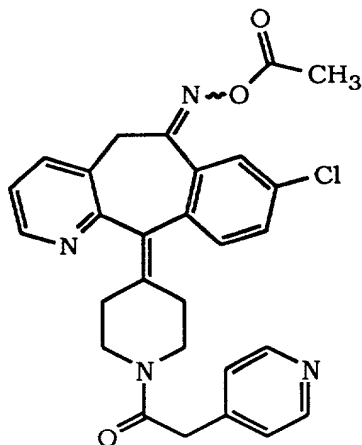
- 5 Follow the procedure of Example 283 except using 4-pyridylacetic acid N-oxide to give the product compound. Mass Spec.:  $MH^+ = 460$

EXAMPLE 419



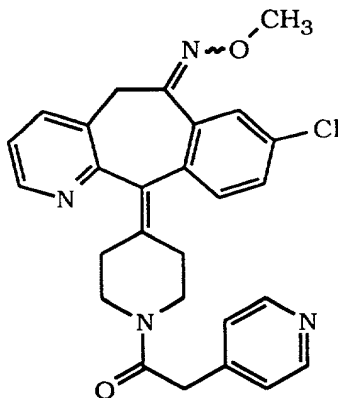
- 10 Dissolve 4.01 g (8.42 mmol) of the compound of Example 410-L in EtOAc and add 14.25 g (63.1 mmol) of finely powdered  $SnCl_2$  dihydrate and stir the mixture for 5 hours. Add 150 mL of saturated NaF (aqueous) and stir for 15 min, then separate the layers and dry the organic phase over  $MgSO_4$ . Filtration and concentrate *in vacuo* to a residue, then
- 15 chromatograph (silica gel, 95%  $CH_2Cl_2/MeOH + NH_4OH$ ) to give 2.95 g of the product compound. Mass Spec.:  $MH^+ = 461$

EXAMPLE 420



- Combine 0.50 g (1.08 mmol) of the compound of Example 419 and  
5 10 mL of anhydrous  $\text{CH}_2\text{Cl}_2$ , and add 0.11 mL (1.62 mmol) of  $\text{CH}_3\text{COCl}$ .  
Add 0.34 mL (4.32 mmol) of pyridine and stir at room temperature for 2.5  
hours. Dilute the mixture with saturated  $\text{NaHCO}_3$  (aqueous), extract with  
 $\text{CH}_2\text{Cl}_2$ , wash the extracts with brine and dry over  $\text{MgSO}_4$ . Concentrate *in*  
*vacuo* to a residue and chromatograph (silica gel, 10%  $\text{MeOH}/\text{CH}_2\text{Cl}_2$  +  
10  $\text{NH}_4\text{OH}$ ) to give 0.271 g of the product compound. Mass Spec.:  $\text{MH}^+ = 503$

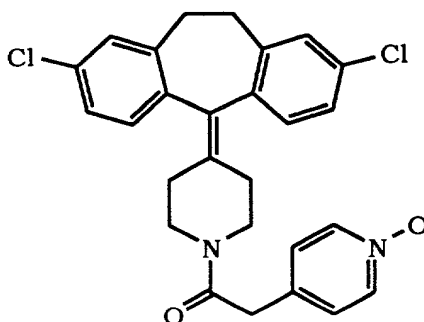
EXAMPLE 421



- 15 Combine 0.65 g (1.41 mmol) of the product compound of Example  
419, 20 mL of  $\text{CH}_2\text{Cl}_2$ , 0.22 mL (3.52 mmol) of methyl iodide, 4.4 mL of  
10%  $\text{NaOH}$  (aqueous) and 68 mg (0.21 mmol) of tetra-*n*-butyl-ammonium  
bromide. Stir the mixture for 5 hours, then separate the layers and dry the  
organic phase over  $\text{MgSO}_4$ . Concentrate *in vacuo* to a residue and

chromatograph (silica gel, 5% MeOH/CH<sub>2</sub>Cl<sub>2</sub> + NH<sub>4</sub>OH) to give 169 mg of the product compound. Mass Spec.: MH<sup>+</sup> = 475

**EXAMPLE 422**



5

Combine 0.1 g (0.21 mmol) of the product compound of Example 411-L and 10 mL of CH<sub>2</sub>Cl<sub>2</sub>, add 0.11 g (0.66 mmol) of MCPBA and stir at ambient temperature for 1 hour. Wash with saturated NaHCO<sub>3</sub> (aqueous), dry over MgSO<sub>4</sub>, and concentrate *in vacuo* to give 0.14 gm of the product compound. m.p.=100°-104°C

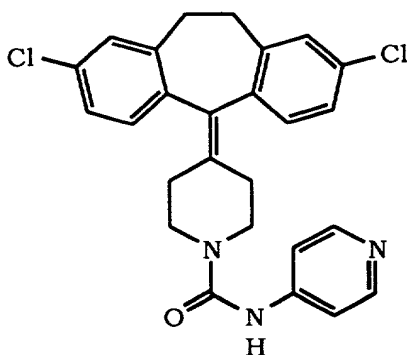
10

Using the starting compound indicated, the following compounds were prepared via substantially the same procedure as described for Example 422:

15

| Starting Compound | Product Compound     | Analytical Data                                 |
|-------------------|----------------------|---|
| Example 423       | <p>Example 422-A</p> | Mass Spec.:<br>(FAB) MH <sup>+</sup> =<br>480.2 |

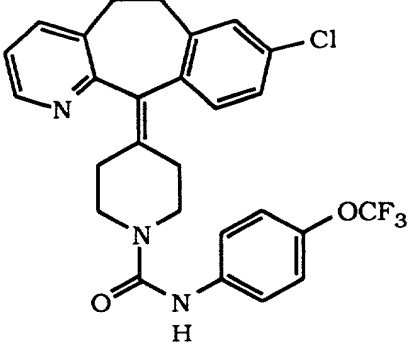
EXAMPLE 423



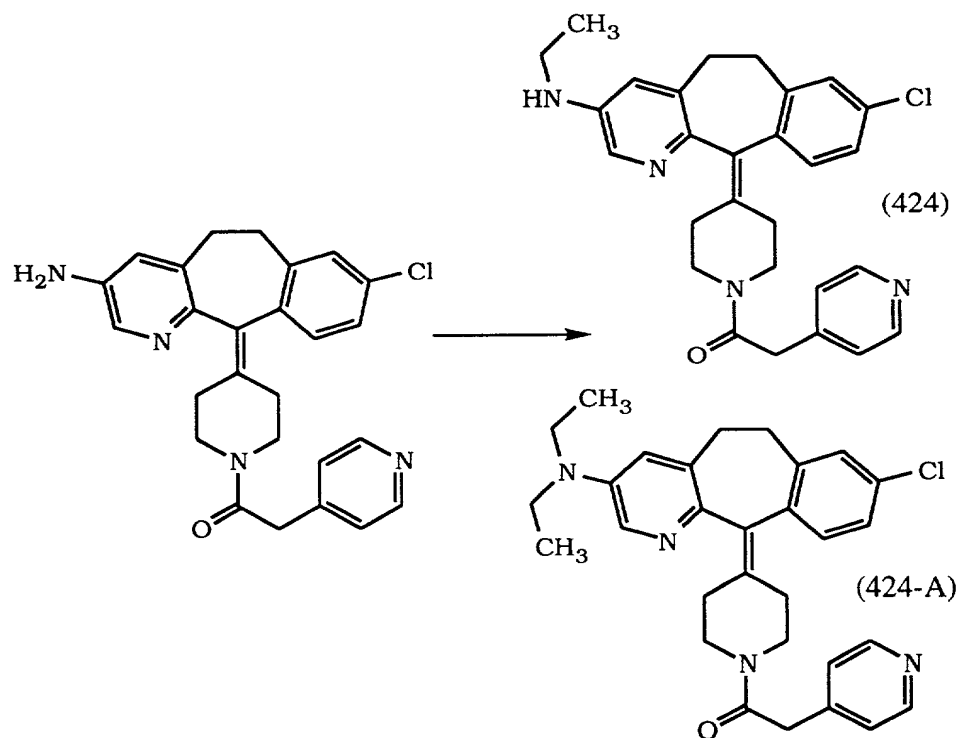
- Combine 0.4 g (1.22 mmol) of the product compound of Preparative Example 59 and 0.2 g (1.2 mmol) of 4-aminopyridylethylcarbamate and heat to 180°C under a dry N<sub>2</sub> atmosphere for 2 hours. Cool the mixture and crystallize the product by adding EtOAc to give 0.49 g of the product compound. m.p.= 206.4°-207 °C; Mass Spec.: (FAB) MH<sup>+</sup> = 464.0

- Using the appropriate ethylcarbamate and the starting compound indicated, the following compounds were prepared via substantially the same procedure as described for Example 423:

| Starting Compound             | Product Compound     | Analytical Data |
|-------------------------------|----------------------|-----------------|
| Preparative Example 1, Step G | <p>Example 423-A</p> | -----           |

|  |  |              |
|--|--|--------------|
| <p>Preparative<br/>Example 1,<br/>Step G</p> |  | <p>-----</p> |
|  | <p>Example 423-B</p>   |              |

#### EXAMPLE 424



- 5            Combine 1 g of the product of Example 402 and 20 mL of MeOH, cool to ~ 0°C, and adjust to pH = 3 by adding 1 N HCl (aqueous). Add 1.25 mL of CH<sub>3</sub>CHO and 1.41 g of NaCNBH<sub>3</sub>, and stir the mixture for 1 hour. Concentrate *in vacuo* to a residue, extract with 100 mL of CH<sub>2</sub>Cl<sub>2</sub> and wash the extract with 100 mL of 10% NaHCO<sub>3</sub>, then with 100 mL of
- 10          water. Dry over MgSO<sub>4</sub>, concentrate *in vacuo* to a residue and chromatograph (silica gel, 1.5% (10% NH<sub>4</sub>OH in MeOH)/CH<sub>2</sub>Cl<sub>2</sub>) to give



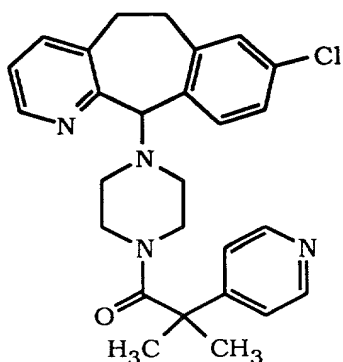
0.158 g of the product compound of Example 424 and 0.198 g of the product compound Example 424-A.

Analytical data for Example 424: Mass Spec.:  $MH^+ = 474$

Analytical data for Example 424-A: Mass Spec.:  $MH^+ = 502$

5

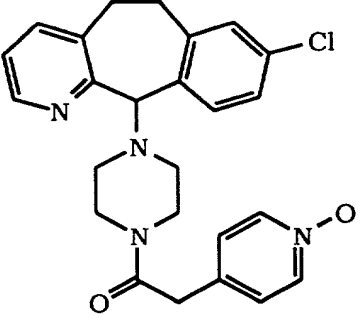
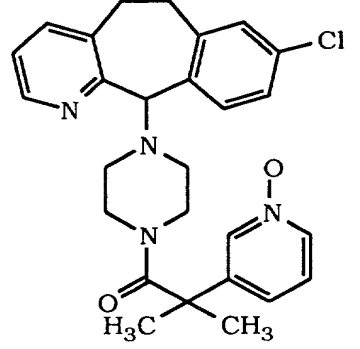
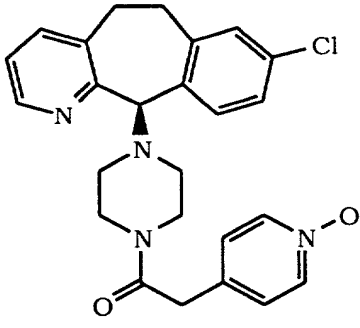
EXAMPLE 425

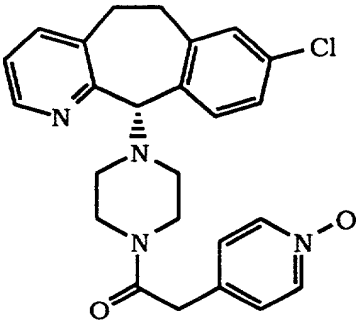
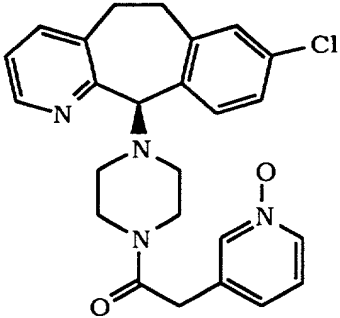
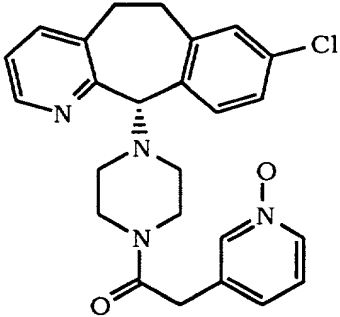


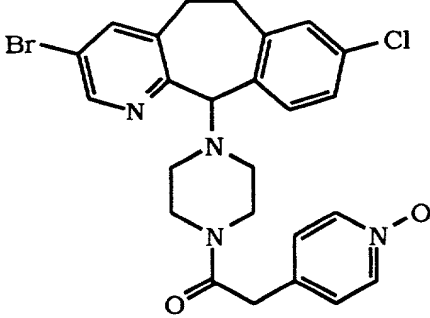
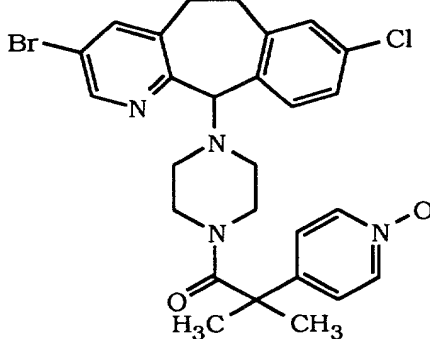
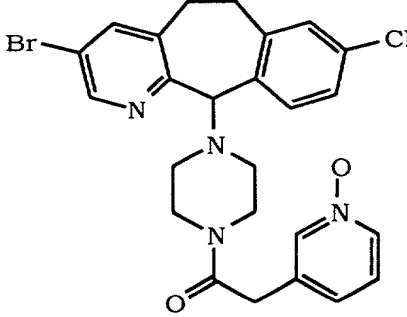
- 10 React the products of Preparative Example 7, Step C and  
Preparative Example 26, via substantially the same procedure as  
described for Example 75 to give the title compound. Mass Spec.:  $MH^+ =$   
461.35

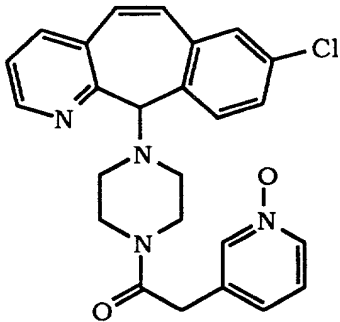
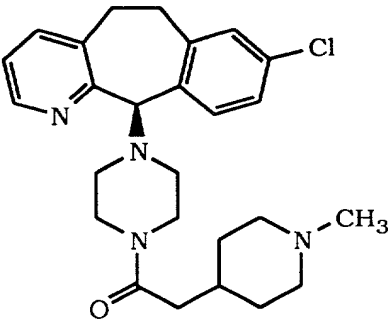
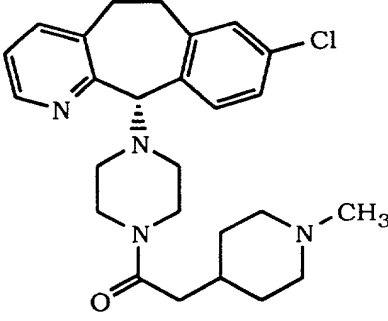
- 15 Using the appropriate carboxylic acid and the starting compound  
indicated, the following compounds were prepared via substantially the  
same procedure as described for Example 425:

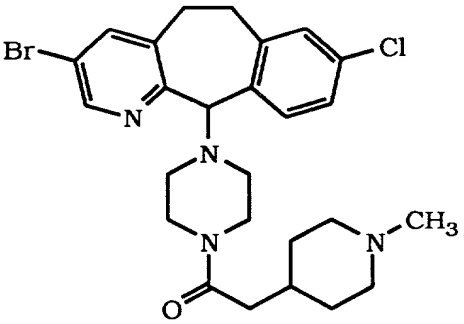
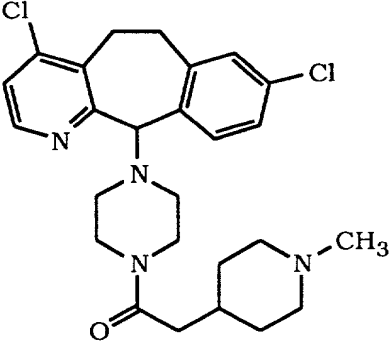
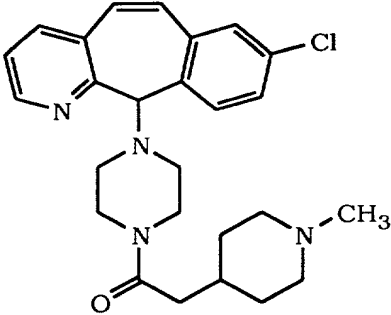
| Starting Compound     | Product Compound     | Analytical Data               |
|-----------------------|----------------------|-------------------------------|
| Preparative Example 7 | <p>Example 425-A</p> | Mass Spec.:<br>$MH^+ = 477.2$ |

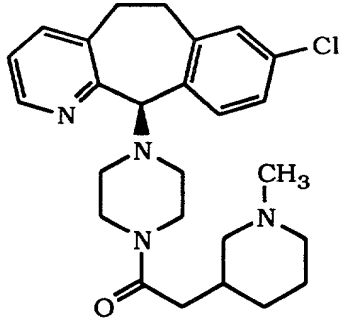
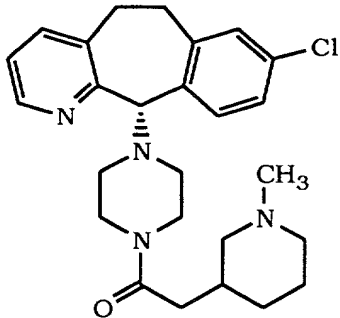
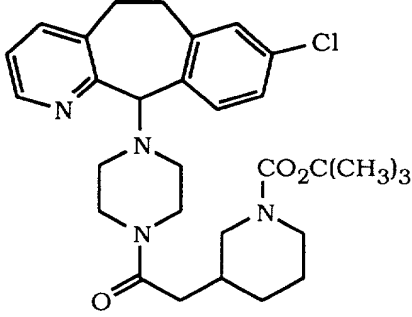
|   |   |   |
|---|---|---|
| <p>Preparative<br/>Example 7</p>                  |  <p>Example 425-B</p>   | <p>Mass Spec.:<br/>MH<sup>+</sup> = 449.3</p> |
| <p>Preparative<br/>Example 7</p>                  |  <p>Example 425-C</p>  | <p>Mass Spec.:<br/>MH<sup>+</sup> = 477.2</p> |
| <p>Preparative<br/>Example 19<br/>R(+)-isomer</p> |  <p>Example 425-D</p> | <p>Mass Spec.:<br/>MH<sup>+</sup> = 449.2</p> |

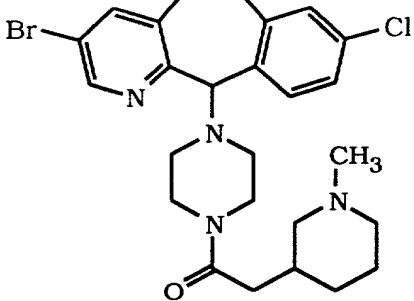
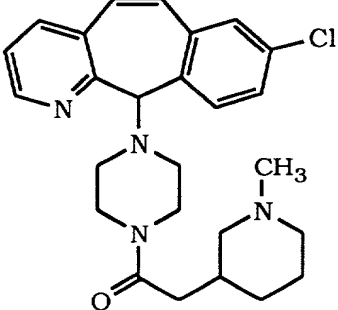
|   |   |   |
|---|---|---|
| <p>Preparative<br/>Example 19<br/>S(-)-isomer</p> |  <p>Example 425-E</p>   | <p>Mass Spec.:<br/>MH<sup>+</sup> = 449.2</p> |
| <p>Preparative<br/>Example 19<br/>R(+)-isomer</p> |  <p>Example 425-F</p>  | <p>Mass Spec.:<br/>MH<sup>+</sup> = 449.3</p> |
| <p>Preparative<br/>Example 19<br/>S(-)-isomer</p> |  <p>Example 425-G</p> | <p>Mass Spec.:<br/>MH<sup>+</sup> = 449.3</p> |

|                                   |   |   |
|-----------------------------------|---|---|
| <p>Preparative<br/>Example 40</p> |  <p>Example 425-H</p>   | <p>Mass Spec.:<br/>MH<sup>+</sup> = 527.0</p> |
| <p>Preparative<br/>Example 40</p> |  <p>Example 425-J</p>  | <p>Mass Spec.:<br/>MH<sup>+</sup> = 555.3</p> |
| <p>Preparative<br/>Example 40</p> |  <p>Example 425-K</p> | <p>Mass Spec.:<br/>MH<sup>+</sup> = 527.1</p> |

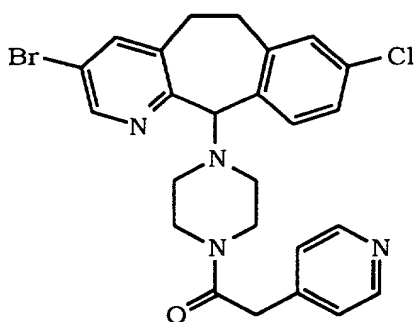
|   |   |   |
|---|---|---|
| <p>Preparative<br/>Example 38</p>                 |  <p>Example 425-L</p>   | <p>Mass Spec.:<br/>MH<sup>+</sup> = 447.2</p> |
| <p>Preparative<br/>Example 19<br/>R(+)-isomer</p> |  <p>Example 425-M</p>  | <p>Mass Spec.:<br/>MH<sup>+</sup> = 453</p>   |
| <p>Preparative<br/>Example 19<br/>S(-)-isomer</p> |  <p>Example 425-N</p> | <p>Mass Spec.:<br/>MH<sup>+</sup> = 453</p>   |

|                                   |   |  |
|-----------------------------------|---|--|
| <p>Preparative<br/>Example 40</p> |  <p>Example 425-O</p>   | <p>Mass Spec.:<br/>MH<sup>+</sup> = 531.25</p> |
| <p>Preparative<br/>Example 41</p> |  <p>Example 425-P</p>  | <p>Mass Spec.:<br/>MH<sup>+</sup> = 487.35</p> |
| <p>Preparative<br/>Example 38</p> |  <p>Example 425-Q</p> | <p>Mass Spec.:<br/>MH<sup>+</sup> = 451.35</p> |

|   |   |  |
|---|---|--|
| <p>Preparative<br/>Example 19<br/>R(+)-isomer</p> |  <p>Example 425-R</p>   | <p>Mass Spec.:<br/>MH<sup>+</sup> = 453.35</p> |
| <p>Preparative<br/>Example 19<br/>S(-)-isomer</p> |  <p>Example 425-S</p>  | <p>Mass Spec.:<br/>MH<sup>+</sup> = 453.35</p> |
| <p>Preparative<br/>Example 7<br/>Step C</p>       |  <p>Example 425-T</p> | <p>Mass Spec.:<br/>MH<sup>+</sup> = 539.45</p> |

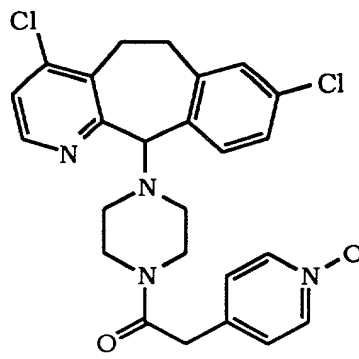
|                                   |   |   |
|-----------------------------------|---|---|
| <p>Preparative<br/>Example 40</p> |  <p>Example 425-U</p> | <p>Mass Spec.:<br/><math>MH^+ = 531.35</math></p> |
| <p>Preparative<br/>Example 38</p> |  <p>Example 425-V</p> | <p>Mass Spec.:<br/><math>MH^+ = 451.4</math></p>  |

EXAMPLE 426

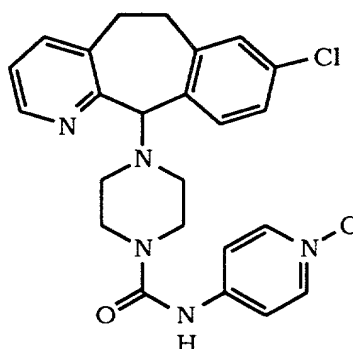


- 5        React the product of Preparative Example 40 and 3-pyridylacetic acid via substantially the same procedure as described for Example 351 to give the title compound. Mass Spec.:  $MH^+ = 511$
- 10      Using the appropriate carboxylic acid and the starting compound indicated, the following compounds were prepared via substantially the same procedure as described for Example 426:



| Starting Compound      | Product Compound  | Analytical Data                        |
|------------------------|---|--|
| Preparative Example 41 |  <p>Example 426-A</p> | Mass Spec.:<br>MH <sup>+</sup> = 483.2 |

#### EXAMPLE 427

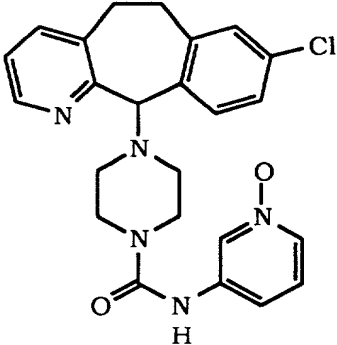
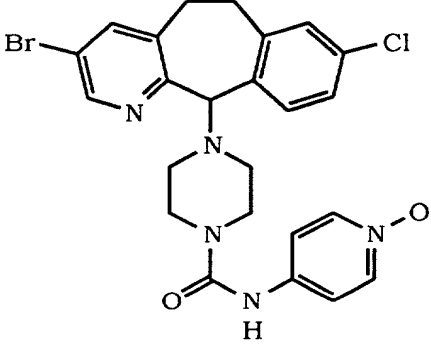
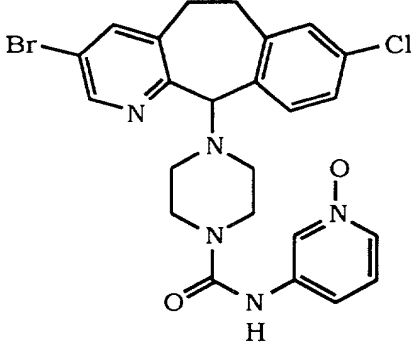


5

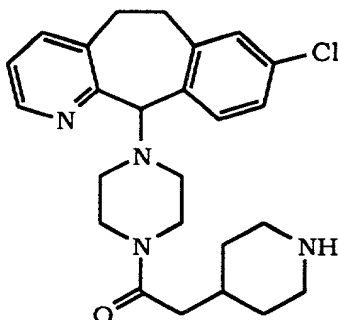
Combine 0.288 g (1.76 mmol) of the product of Preparative Example 63 and 25 mL of anhydrous toluene, heated at (110°C) for 0.5 hours, then cool to 25°C. Add a solution of 0.1 g (0.293 mmol) of the product Preparative Example 7, Step C, in 1.5 mL of anhydrous toluene, and stir at 25°C under an argon atmosphere for 112 hours. Concentrate *in vacuo* to a residue and chromatograph (silica gel, 3%-4% (10% NH<sub>4</sub>OH in MeOH)/CH<sub>2</sub>Cl<sub>2</sub>) to give 0.065 g of the title compound. Mass Spec.: MH<sup>+</sup> = 450.3

Using the appropriate azide and the starting compound indicated, the following compounds were prepared via substantially the same procedure as described for Example 427:

15

| Starting Compound             | Product Compound  | Analytical Data                        |
|-------------------------------|---|--|
| Preparative Example 7, Step C |  <p>Example 427-A</p>    | Mass Spec.:<br>MH <sup>+</sup> = 450.1 |
| Preparative Example 40        |  <p>Example 427-B</p>  | Mass Spec.:<br>MH <sup>+</sup> = 528.1 |
| Preparative Example 40        |  <p>Example 427-C</p> | Mass Spec.:<br>MH <sup>+</sup> = 528.1 |

**EXAMPLE 428**

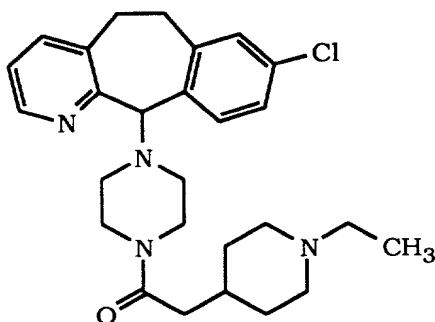


Combine 14.73 g (27.3 mmol) of the compound from Example 193 and 125 mL of anhydrous MeOH, and add (in portions) 300 mL of a 10% solution of concentrated H<sub>2</sub>SO<sub>4</sub> in dioxane. Stir the mixture at 25°C for 2 hours, then pour into water and adjust to pH =13 with 50% NaOH (aqueous). Extract with CH<sub>2</sub>Cl<sub>2</sub>, wash the extract with water and dry over MgSO<sub>4</sub>. Concentrate *in vacuo* to a residue and chromatograph (silica gel, 10% (10% NH<sub>4</sub>OH in MeOH)/CH<sub>2</sub>Cl<sub>2</sub>) to give 8.9 g of the title compound. Mass Spec.: MH<sup>+</sup> = 539

Using the starting compound indicated, the following compounds were prepared via substantially the same procedure as described for Example 428:

| Starting Compound | Product Compound     | Analytical Data                         |
|-------------------|----------------------|---|
| Example 425-T     | <p>Example 428-A</p> | Mass Spec.:<br>MH <sup>+</sup> = 439.45 |

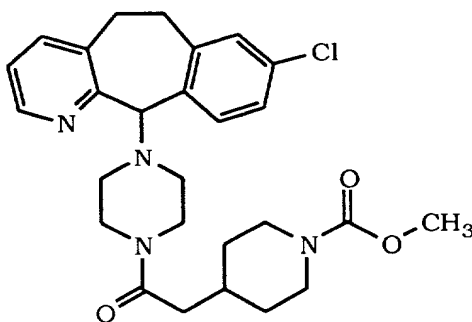
EXAMPLE 429



- Combine 0.5 g (1.14 mmol) of the compound of Example 428 and
- 5 10 mL of 0.6 N HCl in CH<sub>2</sub>Cl<sub>2</sub>, stir for 10 minutes and concentrate *in vacuo* to a residue. Add 20 mL of anhydrous MeOH, then add 0.2006 g (4.56 mmol) of CH<sub>3</sub>CHO, 0.0859 g (1.36 mmol) NaCNBH<sub>3</sub> and 0.5 g of 3A molecular sieves, and heat at 40°C for 115 hours. Filter the mixture, wash the sieves with MeOH and concentrate the combined filtrates *in vacuo* to a
- 10 residue. Dissolve the residue in CH<sub>2</sub>Cl<sub>2</sub> and wash with saturated NaHCO<sub>3</sub> (aqueous), then water and dry over MgSO<sub>4</sub>. Concentrate *in vacuo* to a residue and chromatograph (silica gel, 8% (10% NH<sub>4</sub>OH in MeOH)/CH<sub>2</sub>Cl<sub>2</sub>) to give the title compound. Mass Spec.: MH<sup>+</sup> = 467.3

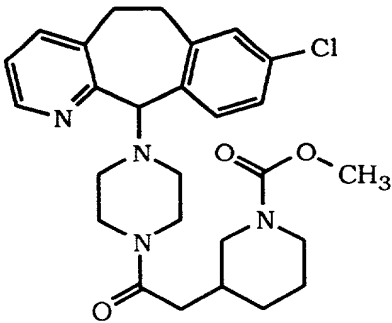
15

EXAMPLE 430



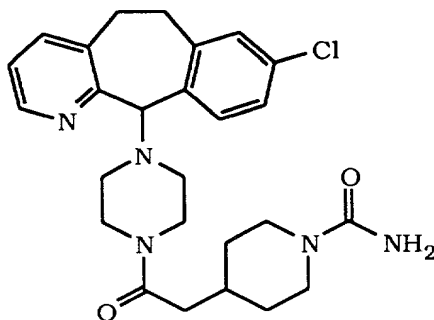
- Combine 0.5 g (1.14 mmol) of the compound of Example 428 and 5
- 20 mL of anhydrous THF, add 0.1076 g (1.14 mmol) ClCO<sub>2</sub>CH<sub>3</sub>, and stir at 25°C for 1 hour. Concentrate *in vacuo* to a residue, add CH<sub>2</sub>Cl<sub>2</sub> and wash with saturated NaHCO<sub>3</sub> (aqueous), then water. Dry the organic phase over MgSO<sub>4</sub>, concentrate *in vacuo* to a residue and chromatograph (silica gel, 1.5% (10% NH<sub>4</sub>OH in MeOH)/CH<sub>2</sub>Cl<sub>2</sub>) to give 0.4213 g of the title compound. Mass Spec.: MH<sup>+</sup> = 497.35

Using the starting compound indicated, the following compounds were prepared via substantially the same procedure as described for Example 430:

| Starting Compound | Product Compound  | Analytical Data                         |
|-------------------|---|---|
| Example 428-A     |  <p>Example 430-A</p> | Mass Spec.:<br>MH <sup>+</sup> = 497.35 |

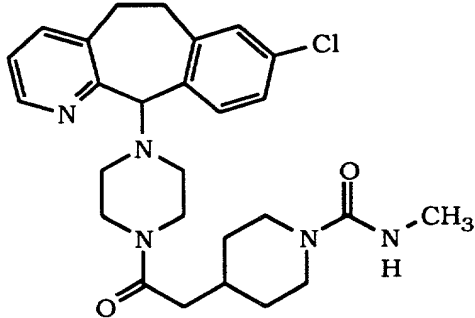
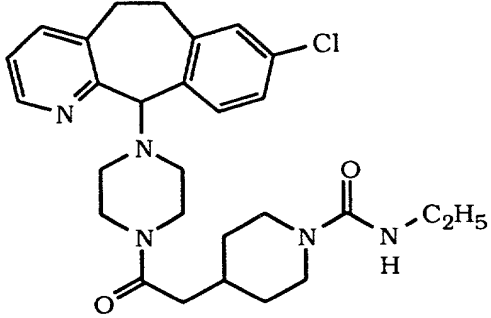
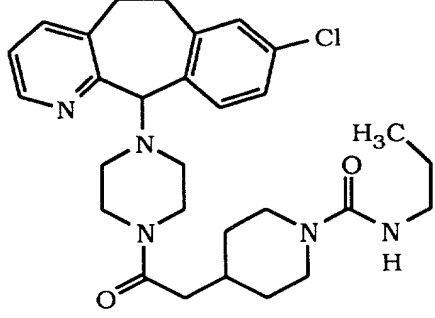
5

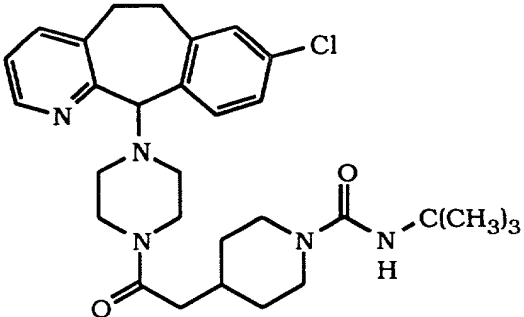
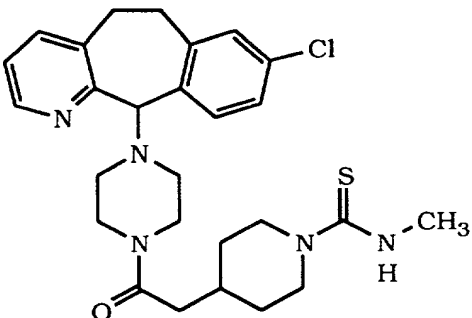
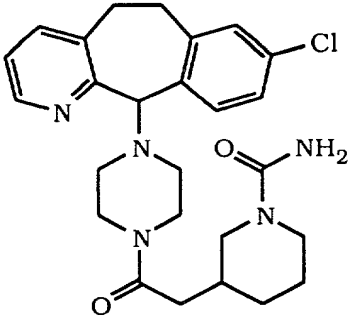
#### EXAMPLE 431

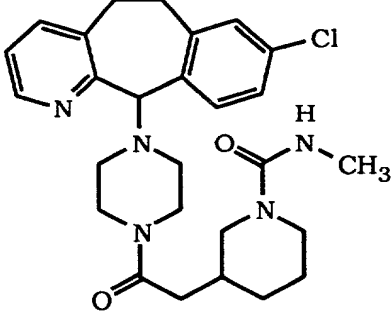


- Combine 0.5 g (1.14 mmol) of the compound of Example 428 and 5 mL of anhydrous CH<sub>2</sub>Cl<sub>2</sub>, add 0.2624 g (2.28 mmol) of trimethylsilylisocyanate and stir under argon at 25°C for 22 hours. Add 0.1312 g (1.14 mmol) of trimethylsilylisocyanate and stir for 8 hours, then dilute with CH<sub>2</sub>Cl<sub>2</sub> and wash with saturated NaHCO<sub>3</sub> (aqueous), then water. Dry over MgSO<sub>4</sub>, concentrate *in vacuo* to a residue and chromatograph (silica gel, 5% (10% NH<sub>4</sub>OH in MeOH)/CH<sub>2</sub>Cl<sub>2</sub>) to give 0.3878 g of the title compound. Mass Spec.: MH<sup>+</sup> = 482.2

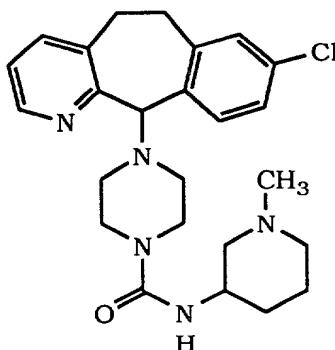
Using the isocyanate (or isothiocyanate) and starting compound indicated, the following compounds were prepared via substantially the same procedure as described for Example 431:

| Starting Compound  | Product Compound  | Analytical Data                                |
|--|---|--|
| <p>CH<sub>3</sub>NCO<br/>and<br/>Example 428</p>                             |  <p>Example 431-A</p>   | <p>Mass Spec.:<br/>MH<sup>+</sup> = 496.45</p> |
| <p>CH<sub>3</sub>CH<sub>2</sub>NCO<br/>and<br/>Example 428</p>               |  <p>Example 431-B</p>  | <p>Mass Spec.:<br/>MH<sup>+</sup> = 510.35</p> |
| <p>CH<sub>3</sub>(CH<sub>2</sub>)<sub>2</sub>NCO<br/>and<br/>Example 428</p> |  <p>Example 431-C</p> | <p>Mass Spec.:<br/>MH<sup>+</sup> = 524.35</p> |

|   |   |  |
|---|---|--|
| <p>(CH<sub>3</sub>)<sub>3</sub>C-NCO<br/>and<br/>Example 428</p>    |  <p>Example 431-D</p>   | <p>Mass Spec.:<br/>MH<sup>+</sup> = 538.35</p> |
| <p>CH<sub>3</sub>NCS<br/>and<br/>Example 428</p>                    |  <p>Example 431-E</p>  | <p>Mass Spec.:<br/>MH<sup>+</sup> = 512.25</p> |
| <p>(CH<sub>3</sub>)<sub>3</sub>Si-NCO<br/>and<br/>Example 428-A</p> |  <p>Example 431-F</p> | <p>Mass Spec.:<br/>MH<sup>+</sup> = 482.3</p>  |

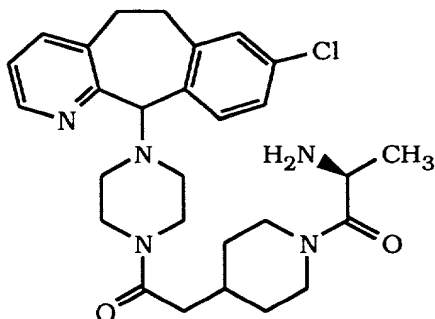
|  |   |  |
|--|---|--|
| <p>CH<sub>3</sub>NCO<br/>and<br/>Example 428-A</p> |  <p>Example 431-G</p> | <p>Mass Spec.:<br/>MH<sup>+</sup> = 496.35</p> |
|--|---|--|

#### EXAMPLE 432



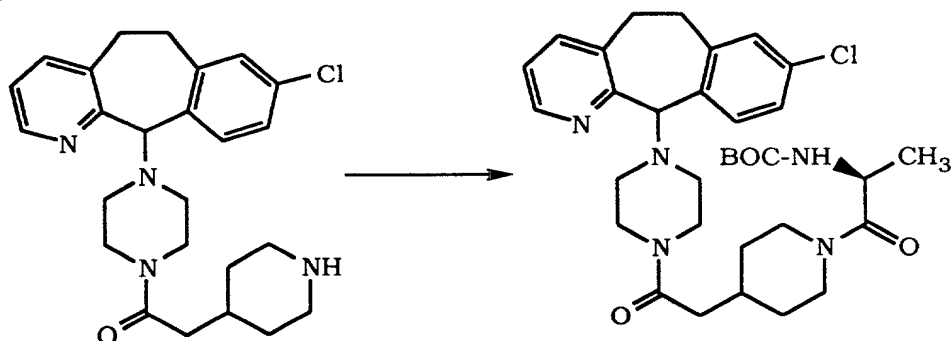
- 5 Combine 0.5 g (1.6 mmol) of the compound of Preparative Example 7 and 1.098 g (6.4 mmol) of the compound from Preparative Example 65 and heat in a sealed vessel at 160°C for 17 hours. Cool the mixture, add CH<sub>2</sub>Cl<sub>2</sub>, wash with water and dry the organic phase over MgSO<sub>4</sub>. Concentrate *in vacuo* to a residue and chromatograph (silica gel, 1.5% (10% NH<sub>4</sub>OH in MeOH)/CH<sub>2</sub>Cl<sub>2</sub>) to give 0.0364 g of the title compound. Mass Spec.: MH<sup>+</sup> = 454.25
- 10

#### EXAMPLE 433



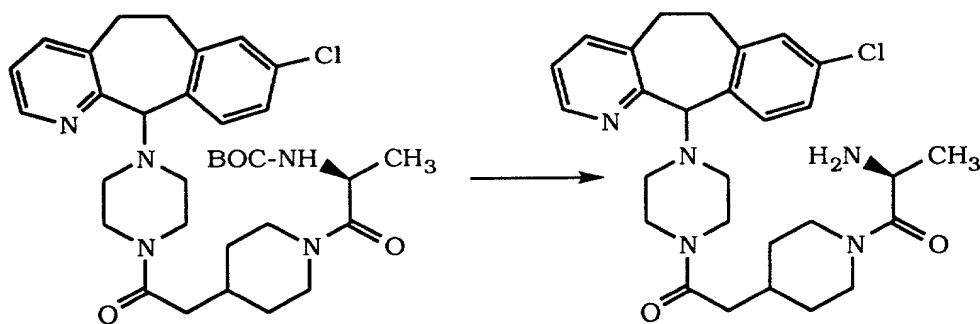


Step A:



- React 0.5 g (1.59 mmol) of the compound of Example 428 and  
5 0.3232 g (2.39 mmol) of N-(tert-butoxycarbonyl)-L-alanine (0.3232 grams)  
(2.39 mmoles) via essentially the same conditions as described in  
Example 425 to give the product compound.

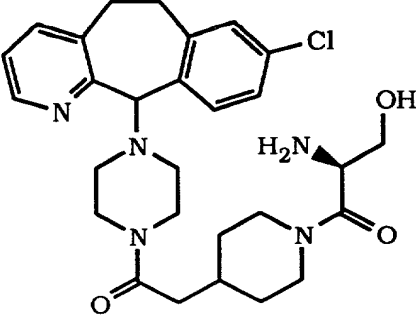
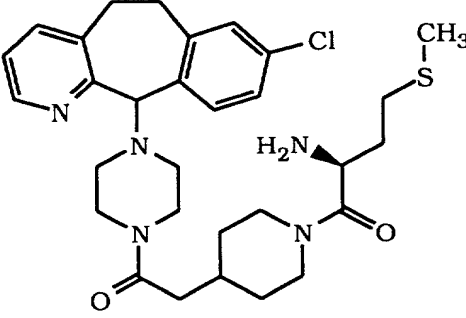
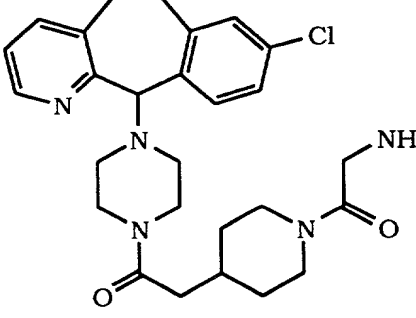
Step B:



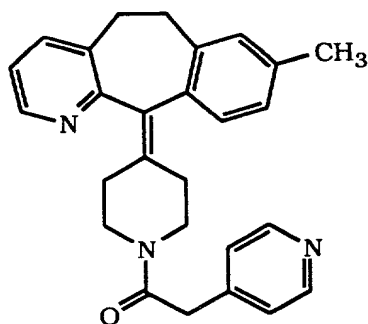
10

- Combine the product of Step A, 5 mL of MeOH and 10 mL of 10%  
concentrated H<sub>2</sub>SO<sub>4</sub> in dioxane and stir at 25°C for 2 hours. Neutralize  
with Biorad AG1X8 (OH<sup>-</sup>) ion exchange resin, filter, wash the resin with 1:1  
MeOH/water and concentrate the filtrate to a residue. Chromatograph the  
15 residue (silica gel, 8% (10% NH<sub>4</sub>OH in MeOH)/CH<sub>2</sub>Cl<sub>2</sub>) to give the title  
compound. Mass Spec.: MH<sup>+</sup> = 510.35

Using the appropriate BOC-amino acid and the starting compound  
indicated, the following compounds were prepared via substantially the  
same procedure as described for Example 433:

| Starting Compound                | Product Compound  | Analytical Data                         |
|----------------------------------|---|---|
| BOC-L-serine and Example 428     |  <p>Example 433-A</p>   | Mass Spec.:<br>MH <sup>+</sup> = 526.2  |
| BOC-L-methionine and Example 428 |  <p>Example 433-B</p>  | Mass Spec.:<br>MH <sup>+</sup> = 570.3  |
| BOC-glycine and Example 428      |  <p>Example 433-C</p> | Mass Spec.:<br>MH <sup>+</sup> = 496.35 |

EXAMPLE 434



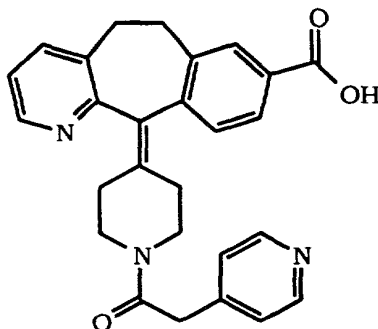
5 React the product of Preparative Example 67 with 4-pyridylacetic acid via essentially the same procedure as described for Example 411 to give the title compound. Mass Spec.:  $MH^+ = 410$

Using the appropriate carboxylic acid and the starting compound indicated, the following compounds were prepared via substantially the same procedure as described for Example 434:

10

| Starting Compound      | Product Compound     | Analytical Data                                    |
|------------------------|----------------------|--|
| Preparative Example 68 | <p>Example 434-A</p> | m.p. = 68.6°-70.3°C<br>Mass Spec.:<br>$MH^+ = 454$ |
|                        |                      |  |

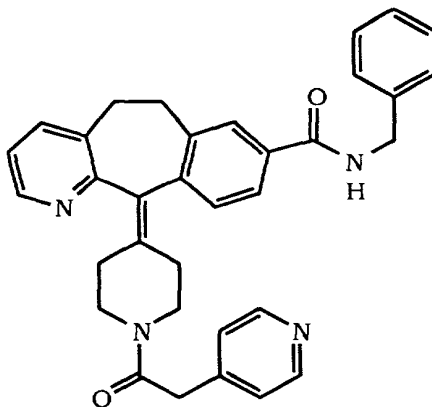
EXAMPLE 435



5 Dissolve 3.04 g (6.7 mmol) of the compound of Example 434-A in 100 mL of MeOH. Add 100 mL of a 12% KOH (aqueous) and stir for one hour at 25°C. Remove the MeOH under vacuum, neutralize to pH 7 with 12 N HCl and concentrate *in vacuo* to a residue. Dry under vacuum and triturate with 10 mL of EtOH, then filter, concentrate the filtrate *in vacuo* to give the title compound. m.p. = 238°-240° C; Mass Spec.: MH<sup>+</sup> = 440

10

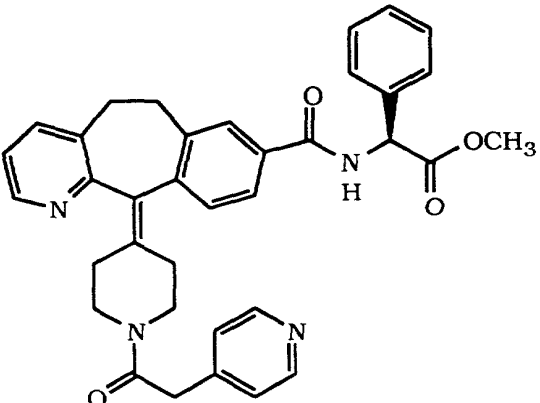
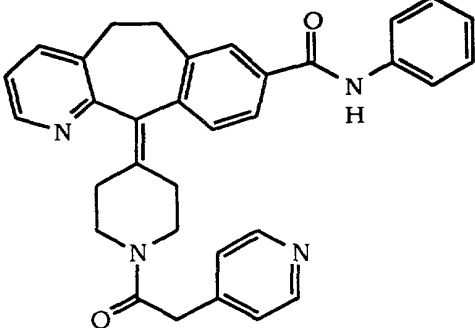
EXAMPLE 436

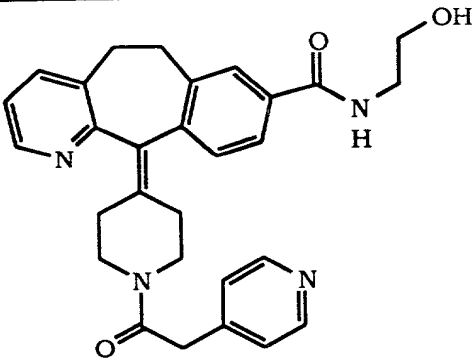
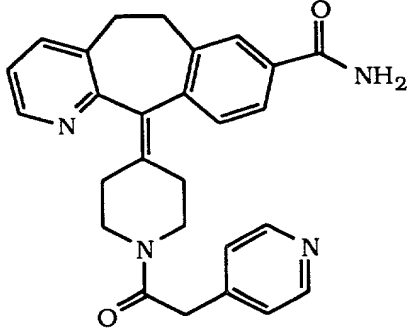


15 Dissolve 0.5 g (1.14 mmol) of the product of Example 435 in 25 mL of DMF, add 0.122 g (1.14 mmol) of benzylamine, 0.33 g (1.7 mmol) of DEC, 0.15 g (1.1 mmol) of HOBT, and 0.23 g (2.27 mmol) of N-methylmorpholine, and stir at 25° C, under nitrogen for 18 hours. Concentrate *in vacuo* to a residue, add 20 mL of water and extract with 50 mL of EtOAc. Dry the organic layer over MgSO<sub>4</sub> and concentrate *in vacuo* to a residue.

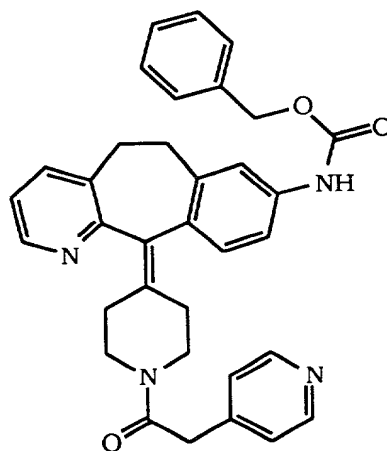
20 Chromatograph (silica gel, 98% CH<sub>2</sub>Cl<sub>2</sub>/MeOH + NH<sub>4</sub>OH) to give the product compound. m.p. = 118°-120° C; Mass Spec.: MH<sup>+</sup> = 529

Using the appropriate amine and the starting compound indicated, the following compounds were prepared via substantially the same procedure as described for Example 436:

| Starting Compound                                   | Product Compound  | Analytical Data   |
|---|---|---|
| <p>S-phenylalanine methyl ester and Example 435</p> |  <p>Example 436-A</p>   | <p>m.p. = 116.9°-118.4°C<br/>Mass Spec.:<br/>MH<sup>+</sup> = 622</p> |
| <p>aniline and Example 435</p>                      |  <p>Example 436-B</p> | <p>m.p. = 137.8°-139.9°C<br/>Mass Spec.:<br/>MH<sup>+</sup> = 516</p> |

|   |  |  |
|---|--|--|
| <p>ethanolamine<br/>and<br/>Example 435</p>     |  <p>Example 436-C</p>  | <p>m.p. = 130.9°-<br/>132.5°C<br/>Mass Spec.:<br/>MH<sup>+</sup> = 482</p> |
| <p>NH<sub>4</sub>Cl<br/>and<br/>Example 435</p> |  <p>Example 436-D</p> | <p>m.p. = 133.2°-<br/>133.5°C<br/>Mass Spec.:<br/>MH<sup>+</sup> = 439</p> |

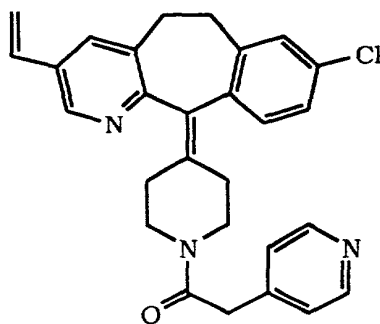
### EXAMPLE 437



- 5 Dissolve 0.18 g (0.41 mmol) of the product of Example 435 in 2 mL of toluene, add 0.12 g (0.43 mmol) of diphenylphosphoryl azide, 0.041 g (0.41 mmol) of Et<sub>3</sub>N, and 0.092 g (0.44 mmol) of benzyl alcohol and heat at reflux under nitrogen for 18 hours. Concentrate *in vacuo* to a residue

and chromatograph (silica gel 95% CH<sub>2</sub>Cl<sub>2</sub>/MeOH) to obtain the title compound. m.p. = 132.8°-133.7°C; MH<sup>+</sup> = 545

EXAMPLE 438



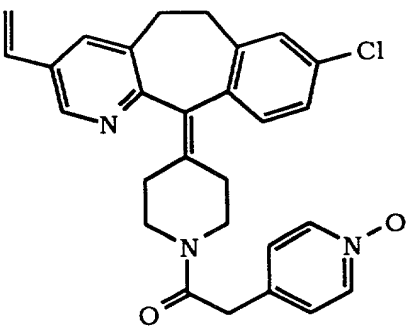
5

React the product of Preparative Example 70 with 4-pyridylacetic acid via essentially the same procedure as described for Example 411 to give the title compound. Mass Spec.: (FAB) MH<sup>+</sup> = 456

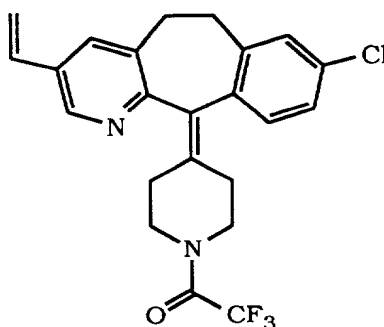
10

Using the appropriate carboxylic acid and the starting compound indicated, the following compounds were prepared via substantially the same procedure as described for Example 438:

| Starting Compound      | Product Compound  | Analytical Data                               |
|------------------------|-------------------|---|
| Preparative Example 70 | <br>Example 438-A | Mass Spec.:<br>(FAB) MH <sup>+</sup> =<br>476 |

|                                   |   |  |
|-----------------------------------|---|--|
| <p>Preparative<br/>Example 70</p> |  <p>Example 438-B</p> | <p>Mass Spec.:<br/>(FAB) <math>MH^+</math> =<br/>472</p> |
|-----------------------------------|---|--|

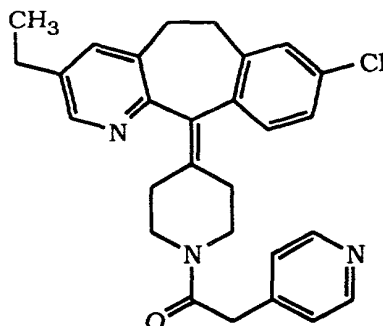
EXAMPLE 439



- 5 Combine 1.7 g (5 mmol) of the product of Preparative Example 70, Step D, and 10 mL of anhydrous pyridine at 0°C under N<sub>2</sub> atmosphere, then slowly add (dropwise) 1 mL (7 mmol) of TFAA and stir at 25°C overnight, Dilute with 100 ml of cold water, extract with CH<sub>2</sub>Cl<sub>2</sub> (2 x 75 mL), wash the extracts successfully with 10% CuSO<sub>4</sub> (aqueous) and
- 10 brine, then dry over MgSO<sub>4</sub>. Concentrate *in vacuo* to a residue and chromatograph (silica gel 30%40% EtOAc/hexane) to give 1.75 g of the title compound. Mass Spec.: (FAB)  $MH^+$  = 433



EXAMPLE 440

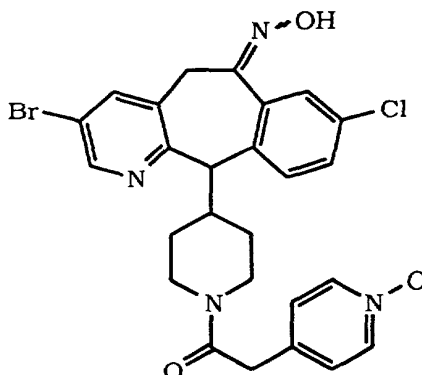


- Combine 0.07 g (0.154 mmol) of the product of Example 438, 7 mL of EtOH and 12 mg of PtO<sub>2</sub>, and hydrogenate at 25°C and atmospheric pressure for 1 hour. Filter, wash with EtOH and concentrate *in vacuo* to give 0.066 g of the title compound. Mass Spec.: (FAB) MH<sup>+</sup> = 458

- Using the starting compound indicated, the following compounds were prepared via substantially the same procedure as described for Example 440:

| Starting Compound | Product Compound     | Analytical Data                               |
|-------------------|----------------------|---|
| Example 438-B     | <p>Example 440-A</p> | Mass Spec.:<br>(FAB) MH <sup>+</sup> =<br>474 |

EXAMPLE 441



- Combine 0.07 g of the compound of Example 410-R, 2 mL of THF,  
5 0.5 mL of water, 10 drops of glacial HOAc, and 0.1 g of powdered Zn, and stir the mixture for 0.5 hours at 25°C. Purify the mixture by preparative thin layer chromatography (Prep TLC), (silica gel, 10% (10% NH<sub>4</sub>OH in MeOH)/CH<sub>2</sub>Cl<sub>2</sub>), to give a total of 68 mg of the crude product. Purify again by Prep TLC), (silica gel, 13% (10% NH<sub>4</sub>OH in MeOH)/CH<sub>2</sub>Cl<sub>2</sub>), to give 33  
10 mg of the product compound. Mass Spec.: MH<sup>+</sup> = 555

ASSAYS

1. In vitro enzyme assays: Inhibition of farnesyl protein  
15 transferase and geranylgeranyl protein transferase.  
Both farnesyl protein transferase (FPT) and geranylgeranyl protein transferase (GGPT) I were partially purified from rat brain by ammonium sulfate fractionation followed by Q-Sepharose (Pharmacia, Inc.) anion exchange chromatography essentially as described by Yokoyama et al  
20 (Yokoyama, K., et al., (1991), A protein geranylgeranyltransferase from bovine brain: Implications for protein prenylation specificity, **Proc. Natl. Acad. Sci USA** 88: 5302-5306, the disclosure of which is incorporated herein by reference thereto). Human farnesyl protein transferase was also expressed in E. coli, using cDNA clones encoding  
25 both the  $\alpha$  and  $\beta$  subunits. The methods used were similar to those published (Omer, C. et al., (1993), Characterization of recombinant human farnesyl protein transferase: Cloning, expression, farnesyl diphosphate binding, and functional homology with yeast prenyl-protein transferases, *Biochemistry* 32:5167-5176). Human farnesyl protein transferase was  
30 partially-purified from the soluble protein fraction of E. coli as described

above. The tricyclic farnesyl protein transferase inhibitors disclosed herein inhibited both human and rat enzyme with similar potencies. Two forms of val<sup>12</sup>-Ha-Ras protein were prepared as substrates for these enzymes, differing in their carboxy terminal sequence. One form  
5 terminated in cysteine-valine-leucine-serine (Ras-CVLS) the other in cysteine-valine-leucine-leucine (Ras-CVLL). Ras-CVLS is a substrate for the farnesyl protein transferase while Ras-CVLL is a substrate for geranylgeranyl protein transferase I. The cDNAs encoding these proteins were constructed so that the proteins contain an amino-terminal extension  
10 of 6 histidine residues. Both proteins were expressed in Escherichia coli and purified using metal chelate affinity chromatography. The radiolabelled isoprenyl pyrophosphate substrates, [<sup>3</sup>H]farnesyl pyrophosphate and [<sup>3</sup>H]geranylgeranyl pyrophosphate, were purchased from DuPont/New England Nuclear.

15 Several methods for measuring farnesyl protein transferase activity have been described (Reiss et al 1990, **Cell** **62**: 81; Schaber et al 1990, **J. Biol. Chem.** **265**: 14701; Manne et al 1990, **PNAS** **87**: 7541; and Barbacid & Manne 1993, U.S. Patent No. 5,185,248). The activity was assayed by measuring the transfer of [<sup>3</sup>H]farnesyl from [<sup>3</sup>H]farnesyl  
20 pyrophosphate to Ras-CVLS using conditions similar to those described by Reiss et al. 1990 (**Cell** **62**: 81). The reaction mixture contained 40 mM Hepes, pH 7.5; 20 mM magnesium chloride; 5 mM dithiothreitol; 0.25 μM [<sup>3</sup>H]farnesyl pyrophosphate; 10 μl Q-Sepharose-purified farnesyl protein transferase; the indicated concentration of tricyclic compound or  
25 dimethylsulfoxide (DMSO) vehicle control (5% DMSO final); and 5 μM Ras-CVLS in a total volume of 100 μl. The reaction was allowed to proceed for 30 minutes at room temperature and then stopped with 0.5 ml of 4% sodium dodecyl sulfate (SDS) followed by 0.5 ml of cold 30% trichloroacetic acid (TCA). Samples were allowed to sit on ice for 45  
30 minutes and precipitated Ras protein was then collected on GF/C filter paper mats using a Brandel cell harvester. Filter mats were washed once with 6% TCA, 2% SDS and radioactivity was measured in a Wallac 1204 Betaplate BS liquid scintillation counter. Percent inhibition was calculated relative to the DMSO vehicle control.

35 The geranylgeranyl protein transferase I assay was essentially identical to the farnesyl protein transferase assay described above, with two exceptions: [<sup>3</sup>H]geranylgeranylpyrophosphate replaced farnesyl pyrophosphate as the isoprenoid donor and Ras-CVLL was the protein

acceptor. This is similar to the assay reported by Casey et al (Casey, P.J., et al., (1991), Enzymatic modification of proteins with a geranylgeranyl isoprenoid, **Proc. Natl. Acad. Sci, USA 88: 8631-8635**, the disclosure of which is incorporated herein by reference thereto).

- 5           2. Cell-Based Assay: Transient expression of val<sup>12</sup>-Ha-Ras-CVLS and val<sup>12</sup>-Ha-Ras-CVLL in COS monkey kidney cells: Effect of farnesyl protein transferase inhibitors on Ras processing and on disordered cell growth induced by transforming Ras.

10           COS monkey kidney cells were transfected by electroporation with the plasmid pSV-SPORT (Gibco/BRL) containing a cDNA insert encoding either Ras-CVLS or Ras-CVLL, leading to transient overexpression of a Ras substrate for either farnesyl protein transferase or geranylgeranyl protein transferase I, respectively (see above).

15           Following electroporation, cells were plated into 6-well tissue culture dishes containing 1.5 ml of Dulbecco's-modified Eagle's media (GIBCO, Inc.) supplemented with 10% fetal calf serum and the appropriate farnesyl protein transferase inhibitors. After 24 hours, media was removed and fresh media containing the appropriate drugs was re-added.

20           48 hours after electroporation cells were examined under the microscope to monitor disordered cell growth induced by transforming Ras. Cells expressing transforming Ras become more rounded and refractile and overgrow the monolayer, reminiscent of the transformed phenotype. Cells were then photographed, washed twice with 1 ml of cold phosphate-buffered saline (PBS) and removed from the dish by scraping  
25           with a rubber policeman into 1 ml of a buffer containing 25 mM Tris, pH 8.0; 1 mM ethylenediamine tetraacetic acid; 1 mM phenylmethylsulfonyl fluoride; 50  $\mu$ M leupeptin; and 0.1  $\mu$ M pepstatin. Cells were lysed by homogenization and cell debris was removed by centrifugation at 2000 x g for 10 min.

30           Cellular protein was precipitated by addition of ice-cold trichloroacetic acid and redissolved in 100  $\mu$ l of SDS-electrophoresis sample buffer. Samples (5-10  $\mu$ l) were loaded onto 14% polyacrylamide minigels (Novex, Inc.) and electrophoresed until the tracking dye neared the bottom of the gel. Proteins resolved on the gels were electroblotted  
35           onto nitrocellulose membranes for immunodetection.

          Membranes were blocked by incubation overnight at 4°C in PBS containing 2.5% dried milk and 0.5% Tween-20 and then incubated with a Ras-specific monoclonal antibody, Y13-259 (Furth, M.E., et al., (1982),

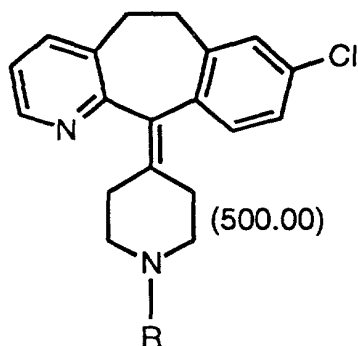
Monoclonal antibodies to the p21 products of the transforming gene of Harvey murine sarcoma virus and of the cellular ras gene family, **J. Virol.** **43: 294-304**), in PBS containing 1% fetal calf serum for one hour at room temperature. After washing, membranes were incubated for one  
5 hour at room temperature with a 1:5000 dilution of secondary antibody, rabbit anti-rat IgG conjugated to horseradish peroxidase, in PBS containing 1% fetal calf serum. The presence of processed and unprocessed Ras-CVLS or Ras-CVLL was detected using a colorimetric peroxidase reagent (4-chloro-1-naphthol) as described by the  
10 manufacturer (Bio-Rad).

### 3. Cell Mat Assay:

Normal human HEPM fibroblasts were planted in 3.5 cm dishes at a density of  $5 \times 10^4$  cells/dish in 2 ml growth medium, and incubated for 3-5d to achieve confluence. Medium was aspirated from each dish and the  
15 indicator tumor cells, T24-BAG4 human bladder carcinoma cells expressing an activated H-ras gene, were planted on top of the fibroblast monolayer at a density of  $2 \times 10^3$  cells/dish in 2 ml growth medium, and allowed to attach overnight. Compound-induced colony inhibition was assayed by addition of serial dilutions of compound directly to the growth  
20 medium 24 h after tumor cell planting, and incubating cells for an additional 14 d to allow colony formation. Assays were terminated by rinsing monolayers twice with phosphate-buffered saline (PBS), fixing the monolayers with a 1% glutaraldehyde solution in PBS, then visualizing tumor cells by staining with X-Gal (Price, J., et al., Lineage analysis in the  
25 vertebrate nervous system by retrovirus-mediated gene transfer, *Proc. Natl. Acad. Sci.* **84**, 156-160(1987)). In the colony inhibition assay, compounds were evaluated on the basis of two  $IC_{50}$  values: the concentration of drug required to prevent the increase in tumor cell number by 50% ( $tIC_{50}$ ) and the concentration of drug required to reduce  
30 the density of cells comprising the cell mat by 50% ( $mIC_{50}$ ). Both  $IC_{50}$  values were obtained by determining the density of tumor cells and mat cells by visual inspection and enumeration of cells per colony and the number of colonies under the microscope. The therapeutic index of the compound was quantitatively expressed as the ratio of  $mIC_{50}/tIC_{50}$ , with  
35 values greater than one indicative of tumor target specificity.

RESULTS OF ASSAYS - TABLES 7 TO 28

The compounds listed in Table 7 refer to compounds of Formula 500.00:



5

TABLE 7

| EXAMPLE | R | FPT IC <sub>50</sub> (μM) |
|---------|---|---------------------------|
| 1       |   | 0.25                      |
| 2       |   | 0.47                      |
| 3       |   | 0.66                      |
| 88      |   | 1.0                       |
| 4       |   | 1.0<br>0.8                |
| 53      |   | 1.5                       |

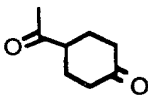
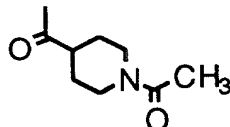
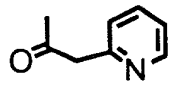
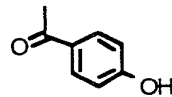
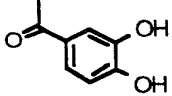
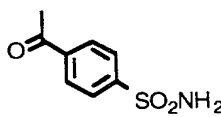
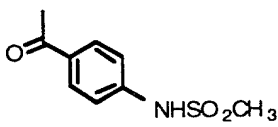
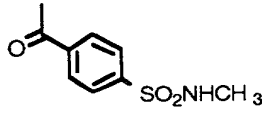
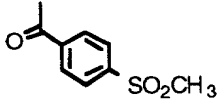
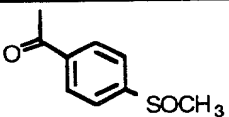
|    |   |     |
|----|---|-----|
| 5  |  | 1.7 |
| 89 |  | 1.8 |
| 6  |  | 2.0 |
| 7  |  | 2.3 |

Table 7 continued

| EXAMPLE | R   | FPT IC <sub>50</sub> (μM) |
|---------|---|---------------------------|
| 8       |  | 2.3                       |
| 90      |  | 3.4                       |
| 91      |  | 3.9                       |
| 92      |  | 3.9                       |
| 93      |  | 3.9                       |
| 94      |  | 4.0                       |

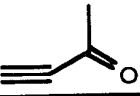
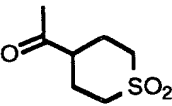
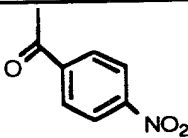
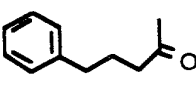
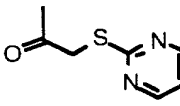
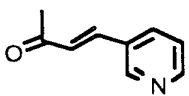
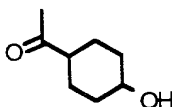
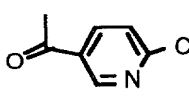
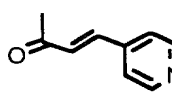
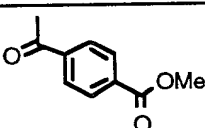
|    |   |     |
|----|---|-----|
| 9  |  | 4.0 |
| 95 |  | 4.2 |
| 10 |  | 4.3 |
| 11 |  | 4.3 |
| 12 |  | 4.3 |

TABLE 7 - continued

| EXAMPLE | R   | FPT IC <sub>50</sub> (μM) |
|---------|---|---------------------------|
| 96      |  | 4.3                       |
| 97      |  | 4.4                       |
| 98      |  | 4.4                       |
| 99      |  | 4.4                       |
| 13      |  | 4.5                       |



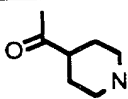
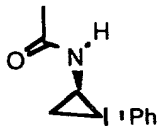
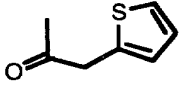
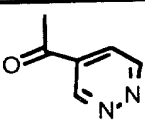
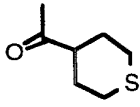
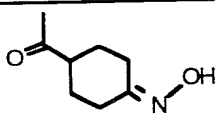
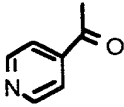
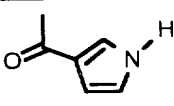
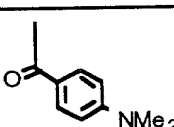
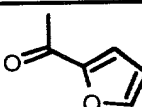
|     |  |     |
|-----|--|-----|
| 100 |   | 4.5 |
| 101 |   | 4.6 |
| 102 |   | 4.6 |
| 14  |   | 4.6 |
| 103 |   | 4.6 |
| 104 |  | 4.7 |

TABLE 7 - continued

| EXAMPLE | R   | FPT IC <sub>50</sub> (μM) |
|---------|---|---------------------------|
| 15      |  | 4.7                       |
| 16      |  | 4.8                       |
| 17      |  | 4.8                       |
| 52      |  | 4.9                       |

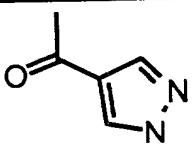
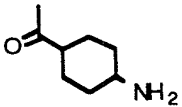
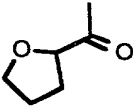
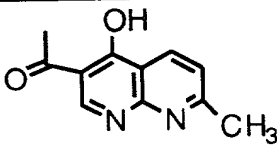
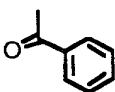
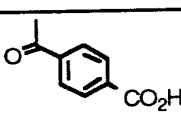
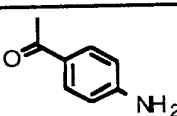
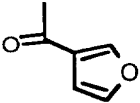
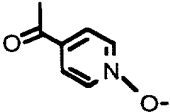
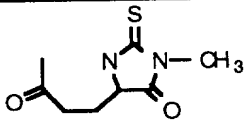
|     |   |     |
|-----|---|-----|
| 18  |    | 4.9 |
| 105 |    | 5.0 |
| 19A |    | 5.1 |
| 20  |    | 5.2 |
| 54  |    | 5.3 |
| 106 |   | 5.3 |
| 21  |  | 5.9 |

TABLE 7 - continued

| EXAMPLE | R   | FPT IC <sub>50</sub> (μM) |
|---------|---|---------------------------|
| 55      |  | 5.9                       |
| 22      |  | 6.0                       |
| 23      |  | 6.0                       |

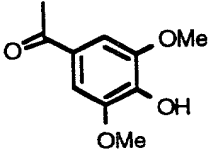
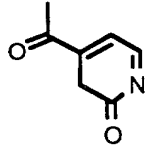
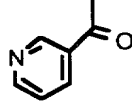
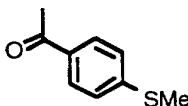
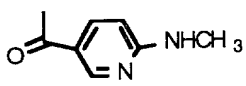
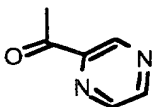
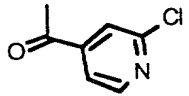
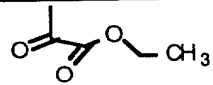
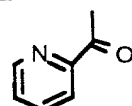
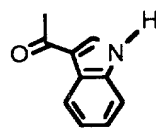
|     |   |      |
|-----|---|------|
| 24  |    | 6.2  |
| 25  |    | 6.25 |
| 26  |    | 6.3  |
| 108 |    | 6.9  |
| 109 |    | 7.2  |
| 27  |   | 7.3  |
| 28  |  | 7.3  |

TABLE 7 - continued

| EXAMPLE | R   | FPT IC <sub>50</sub> (μM) |
|---------|---|---------------------------|
| 56      |  | 7.9                       |
| 29      |  | 8.0                       |
| 30      |  | 5.7                       |

|     |  |     |
|-----|--|-----|
| 31  |  | 8.3 |
| 110 |  | 8.3 |
| 111 |  | 8.5 |
| 32  |  | 8.7 |
| 33  |  | 8.7 |
| 112 |  | 8.8 |
| 34  |  | 9.8 |

TABLE 7 - continued

| EXAMPLE | R | FPT IC <sub>50</sub> (μM) |
|---------|---|---------------------------|
| 57      |   | 9.8                       |
| 35      |   | 9.9                       |
| 113     |   | 10.3                      |

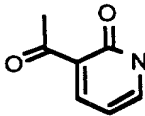
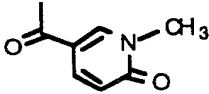
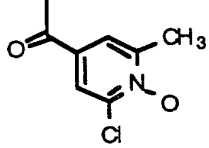
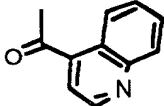
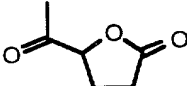
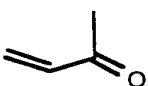
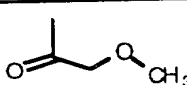
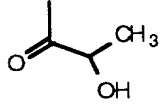
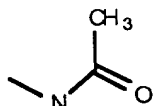
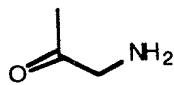
|     |   |      |
|-----|---|------|
| 114 |    | 11.1 |
| 36  |    | 11.2 |
| 37  |    | 11.4 |
| 38  |    | 12.1 |
| 39  |    | 13.4 |
| 115 |   | 14.2 |
| 58  |  | 14.4 |

TABLE 7 - continued

| EXAMPLE | R   | FPT IC <sub>50</sub> (μM) |
|---------|---|---------------------------|
| 116     |  | 15.7                      |
| 117     |  | 16.2                      |
| 118     |  | 22.3                      |

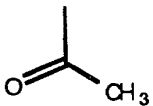
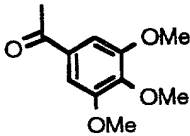
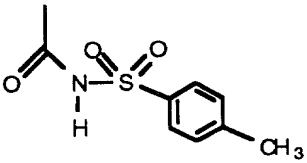
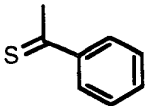
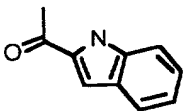
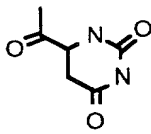
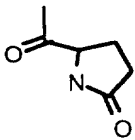
|     |   |                  |
|-----|---|------------------|
| 59  |    | 26.9             |
| 119 |    | 41% at<br>11μM   |
| 120 |   | 4% at<br>39μM    |
| 121 |    | 1.4              |
| 40  |    | 44% at<br>13μM   |
| 122 |  | 23% at<br>12.5μM |
| 123 |  | 23% at<br>12.6μM |

TABLE 7 - continued

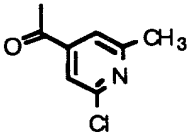
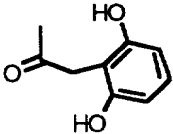
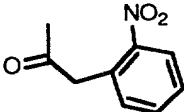
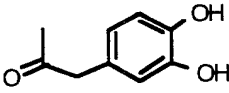
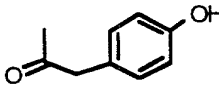
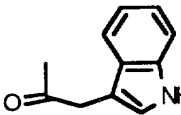
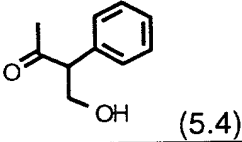
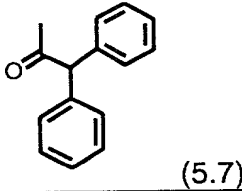
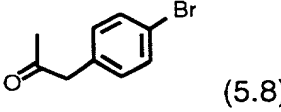
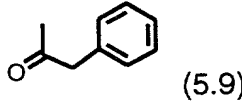
| EXAMPLE | R  | FPT IC <sub>50</sub> (μM) |
|---------|--|---------------------------|
| 124     |     | 37% at<br>12.8μM          |
| 125     |     | 10.3                      |
| 126     |     | 2.9                       |
| 127     |     | 3.5<br>2.7                |
| 128     |    | 3.0                       |
| 129     |   | 32% at<br>11.8μM          |
| 41      |   | 6.1                       |
| 42      |   | 0.6                       |
| 43      |  | 0.6                       |
| 44      |   | 0.8                       |

TABLE 7 - continued

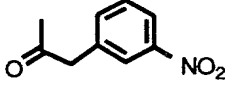
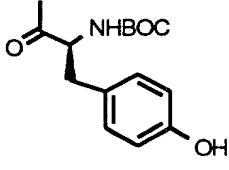
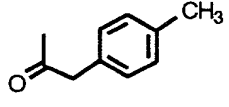
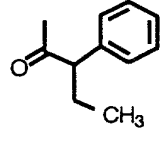
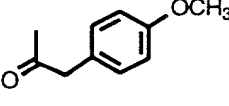
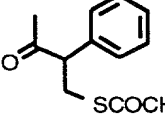
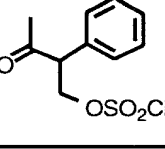
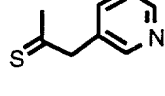
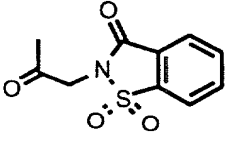
| EXAMPLE | R  | FPT IC <sub>50</sub> (μM) |
|---------|--|---------------------------|
| 45      |  (5.11)   | 1.2<br>0.87               |
| 46      |  (5.12)   | 1.2                       |
| 47      |  (5.13)   | 1.3<br>1.01               |
| 48      |  (5.14)   | 1.3                       |
| 49      |  (5.15) | 1.4                       |
| 84      |  (5.5)  | 0.29                      |
| 83      |  (5.6)  | 0.59                      |
| 19      |  (5.10) | 1.0                       |
| 85      |  (5.16) | 2.0                       |



TABLE 7 - continued

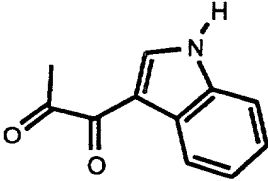
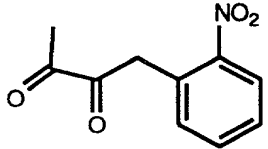
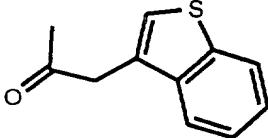
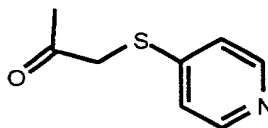
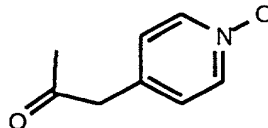
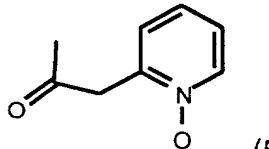
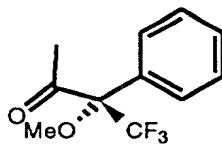
| EXAMPLE | R  | FPT IC <sub>50</sub> (μM) |
|---------|--|---------------------------|
| 219     | <br>(5.92)    | 6.64                      |
| 220     | <br>(5.93)    | 2.49                      |
| 221     | <br>(5.94)    | 3.71                      |
| 222     | <br>(5.95)  | 0.38                      |
| 227     | <br>(5.102) | 0.53                      |
| 228     | <br>(5.103) | 7.5                       |
| 287     |             | 0.72<br>5.02              |

TABLE 7 - continued

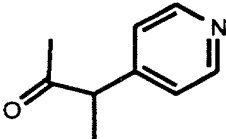
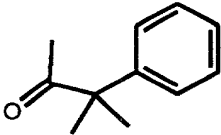
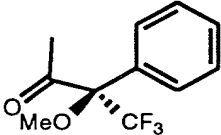
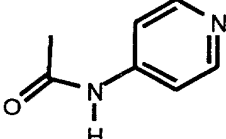
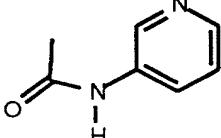
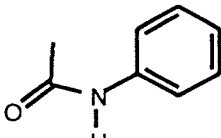
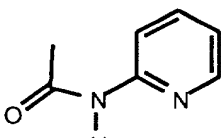
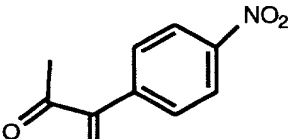
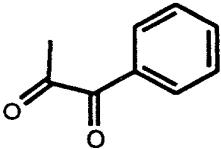
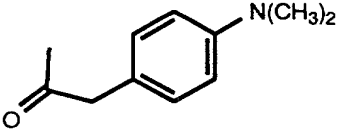
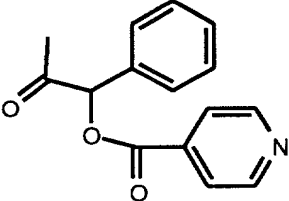
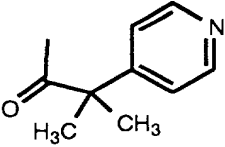
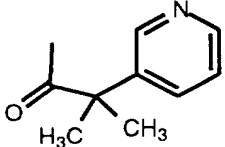
| EXAMPLE | R   | FPT IC <sub>50</sub> (μM) |
|---------|---|---------------------------|
| 288     |    | 1.11                      |
| 289     |    | 1.44<br>1.4               |
| 290     |    | 3.8<br>2.55               |
| 291     |   | 0.87                      |
| 292     |  | 0.99                      |
| 293     |  | 1.76<br>0.47              |
| 294     |  | 2.11                      |
| 295     |  | 2.4                       |

TABLE 7 - continued

| EXAMPLE | R   | FPT IC <sub>50</sub> (μM) |
|---------|---|---------------------------|
| 296     |    | 4.1                       |
| 297     |   | 2.71                      |
| 298     |    | 4.58                      |
| 299     |   | 1.34                      |
| 300     |  | 0.96                      |

The compounds listed in Table 8 refer to compounds of Formula 505.00:

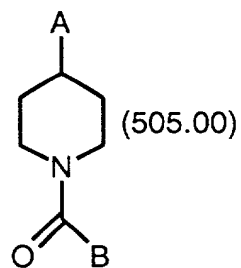


TABLE 8

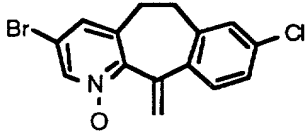
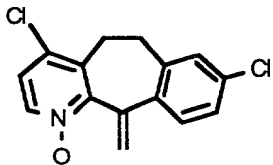
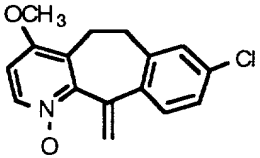
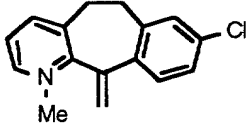
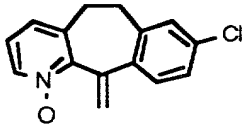
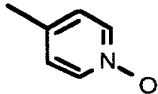
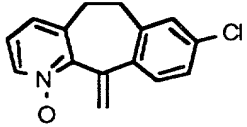
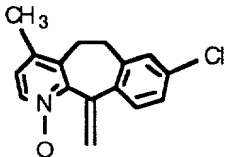
| EXAMPLE | A   | B   | FPT<br>IC <sub>50</sub><br>(μM) |
|---------|---|---|---------------------------------|
| 74B     |    | CH <sub>3</sub>   | 4.0                             |
| 74C     |    | CH <sub>3</sub>   | 11.6                            |
| 74A     |    | CH <sub>3</sub>   | 25% at<br>14.2μM                |
| 130     |   | CH <sub>3</sub>   | 7% at<br>12.1μM                 |
| 131     |  |  | 16% at<br>13.4μM                |
| 73      |  | CH <sub>3</sub>   | 27% at<br>15.6μM                |
| 132     |  | CH <sub>3</sub>   | 22% at<br>15μM                  |

TABLE 8 - continued

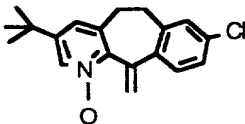
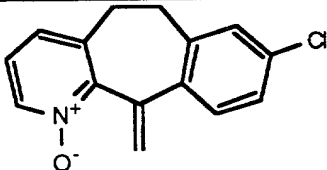
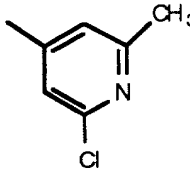
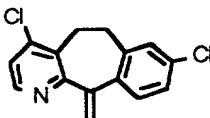
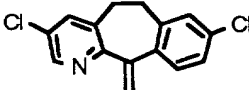
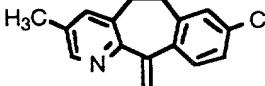
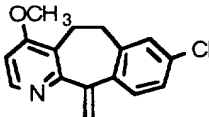
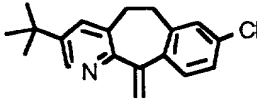
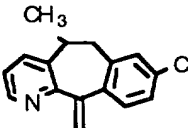
| EXAMPLE | A   | B   | FPT<br>IC <sub>50</sub><br>(μM) |
|---------|---|---|---------------------------------|
| 133     |    | CH <sub>3</sub>   | 16% at<br>14.1 μM               |
| 134     |    |  | 7% at<br>12.2 μM                |
| 135     |    | CH <sub>3</sub>   | 7.7                             |
| 62      |   | CH <sub>3</sub>   | 7.8                             |
| 64      |  | CH <sub>3</sub>   | 10.6                            |
| 136     |  | CH <sub>3</sub>   | 11.5                            |
| 66      |  | CH <sub>3</sub>   | 22% at<br>50 μM                 |
| 137     |  | CH <sub>3</sub>   | 15% at<br>16.3 μM               |

TABLE 8 - continued

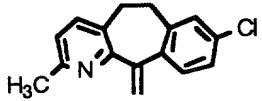
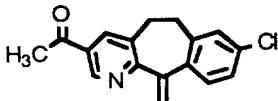
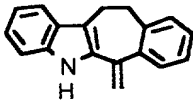
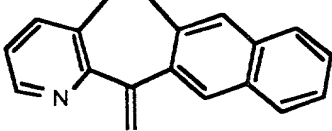
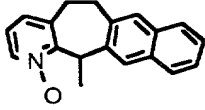
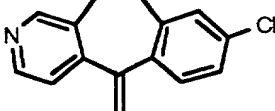
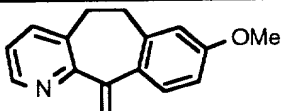
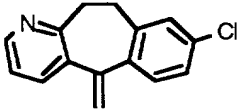
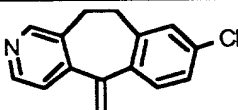
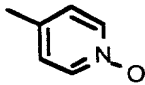
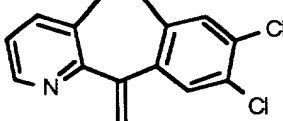
| EXAMPLE | A   | B   | FPT<br>IC <sub>50</sub><br>(μM) |
|---------|---|---|---------------------------------|
| 63      |    | CH <sub>3</sub>   | 1% at<br>16.4μM                 |
| 139     |    | CH <sub>3</sub>   | 37% at<br>15.2μM                |
| 140     |    | CH <sub>3</sub>   | 15.7                            |
| 71A     |   | CH <sub>3</sub>   | 17.6                            |
| 141     |  | CH <sub>3</sub>   | 29% at<br>50μM                  |
| 143     |  | CH <sub>3</sub>   | 35.4                            |
| 71B     |  | CH <sub>3</sub>   | 56.0                            |
| 144     |  | CH <sub>3</sub>   | 30% at<br>50μM                  |
| 144a    |  |  | 47% at<br>46μM                  |
| 71C     |  | CH <sub>3</sub>   | 38% at<br>15.5μM                |

TABLE 8 - continued

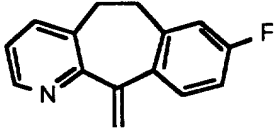
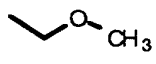
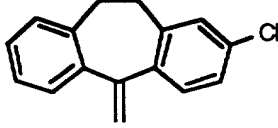
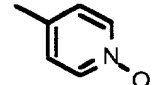
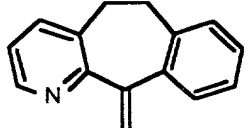
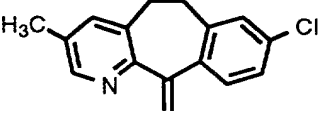
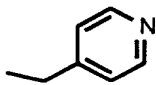
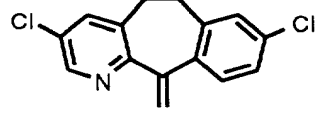
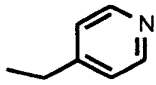
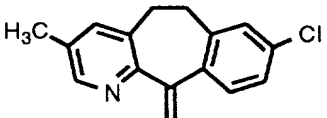
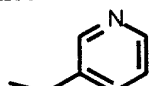
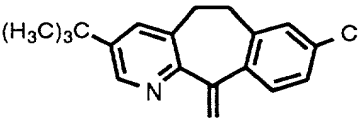
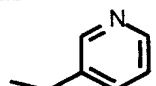
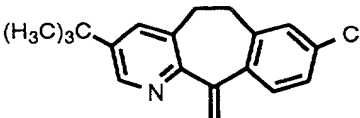
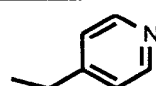
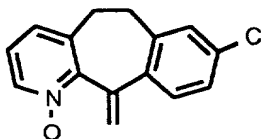
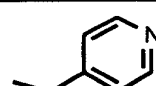
| EXAMPLE | A   | B   | FPT<br>IC <sub>50</sub><br>(μM) |
|---------|---|---|---------------------------------|
| 145     |    |    | >10                             |
| 146     |    |    | 45% at<br>12μM                  |
| 147     |    | CH <sub>3</sub>   | 0% at<br>18.8μM                 |
| 301     |   |   | 0.04<br>0.075                   |
| 180     |  |  | 0.072<br>0.04                   |
| 303     |  |  | 0.55                            |
| 304     |  |  | 2.63                            |
| 305     |  |  | 40%<br>@<br>4μM                 |
| 230     |  |  | 2.06                            |

TABLE 8 - continued

| EXAMPLE | A | B | FPT<br>IC <sub>50</sub><br>(μM) |
|---------|---|---|---------------------------------|
| 307     |   |   | 0.22<br>0.14                    |
| 235     |   |   | 3.57                            |
| 309     |   |   | 0.93                            |
| 310     |   |   | 3.6                             |
| 311     |   |   | 0.61                            |
| 323     |   |   | 4.9                             |
| 5.39    |   |   | 2.3                             |
| 358     |   |   | 0.57                            |



TABLE 8 - continued

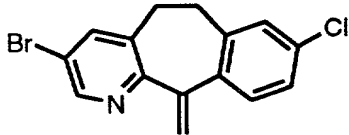
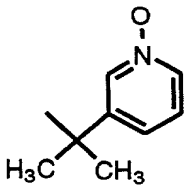
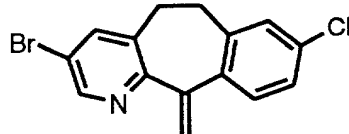
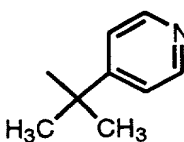
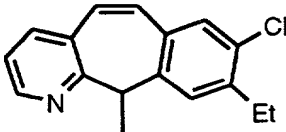
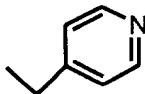
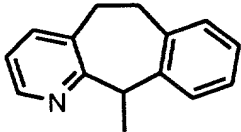
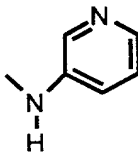
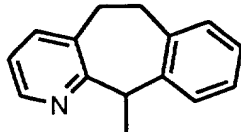
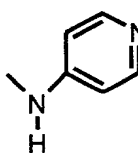
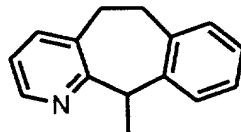
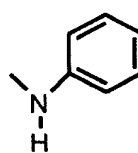
| EXAMPLE | A   | B   | FPT<br>IC <sub>50</sub><br>(μM) |
|---------|---|---|---------------------------------|
| 360     |    |    | 0.59                            |
| 361     |    |    | 0.32                            |
| 362     |   |   | 1.16                            |
| 365     |  |  | 5.0                             |
| 366     |  |  | 4.0                             |
| 367     |  |  | 3.3                             |

Table 9 lists FPT IC<sub>50</sub> results for additional compounds.

TABLE 9

| EXAMPLE        | FPT IC <sub>50</sub><br>(μM) | EXAMPLE        | FPT IC <sub>50</sub><br>(μM) | EXAMPLE        | FPT IC <sub>50</sub><br>(μM) |
|----------------|------------------------------|----------------|------------------------------|----------------|------------------------------|
| 229<br>(5.104) | 4.38                         | 231<br>(5.106) | 44% @<br>12 μM               | 232<br>(5.107) | 6.0                          |
| 236<br>(5.111) | 1.48                         | 237<br>(5.112) | 18% @<br>4 μM                | 238<br>(5.113) | 26% @<br>4 μM                |
| 239<br>(5.114) | 1.75                         | 240<br>(5.115) | 3.12                         | 246<br>(5.121) | 0.06                         |
| 247<br>(5.122) | 0.16                         | 248<br>(5.124) | 1.2                          | 248<br>(5.123) | 0.19                         |
| 249<br>(5.125) | 0.64                         | 250<br>(5.126) | 0.95                         | 256<br>(5.132) | 4.9                          |
| 257<br>(5.133) | 2.3                          | 258<br>(5.134) | 10.8                         | 259<br>(5.135) | 2.2                          |
| 260<br>(5.136) | 9.9                          | 266<br>(5.138) | 0.46                         | 269<br>(5.140) | 0.72<br>0.46                 |
| 276<br>(5.145) | 1.77                         | 279<br>(5.147) | 7.7                          | 280<br>(5.148) | 23                           |
| 281<br>(5.149) | 2.9                          | 282<br>(5.150) | 4.5                          | 283<br>(5.151) | 0.48<br>0.55                 |
| 284<br>(5.152) | 4.3                          | 285<br>(5.153) | 0.76                         | 286<br>(5.154) | 1.5                          |
| 278            | 0.88                         | 274            | 0.91<br>1.38                 | 270            | 2.8                          |

The compounds listed in Table 10 refer to compounds of Formula

5 510.00:

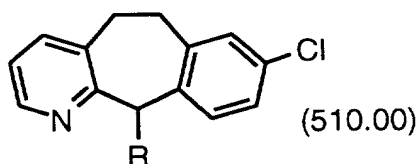


TABLE 10

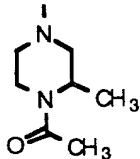
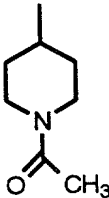
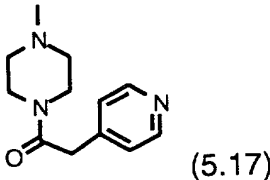
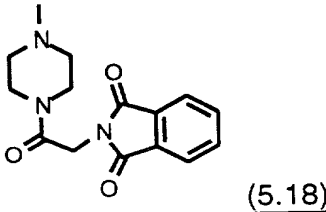
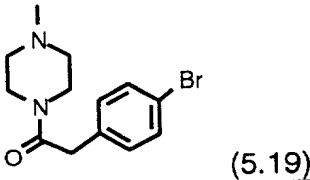
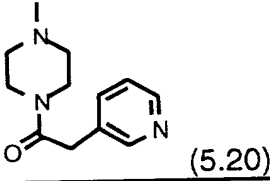
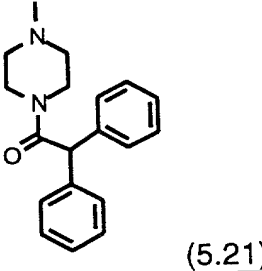
| EXAMPLE | R  | FPT IC <sub>50</sub> (μM) |
|---------|--|---------------------------|
| 149     |               | 10.8                      |
| 150     |               | 38% at<br>16.9μM          |
| 75      | <br>(5.17)   | 0.36<br>0.16              |
| 76      | <br>(5.18)  | 0.82                      |
| 77      | <br>(5.19) | 2.04                      |
| 78      | <br>(5.20) | 1.0<br>0.42               |
| 79      | <br>(5.21) | 2.5                       |

TABLE 10 - continued

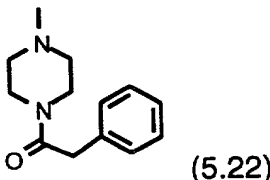
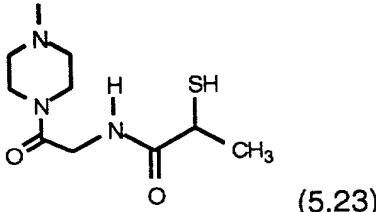
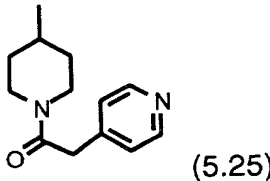
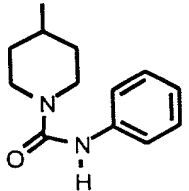
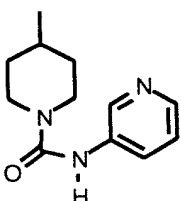
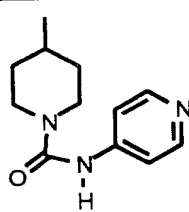
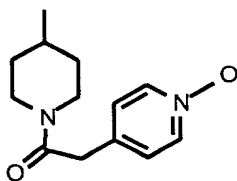
| EXAMPLE | R   | FPT IC <sub>50</sub> (μM) |
|---------|---|---------------------------|
| 80      | <br>(5.22)   | 2.73                      |
| 81      | <br>(5.23)  | 2.78                      |
| 82      | <br>(5.25)   | 0.16<br>0.36              |
| 312     | <br>(5.25) | 0.9                       |
| 313     | <br>(5.25) | 0.97                      |
| 314     | <br>(5.25) | 0.83                      |
| 234     | <br>(5.25) | 0.33                      |

TABLE 10 - continued

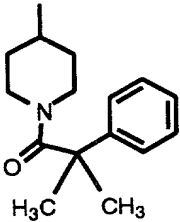
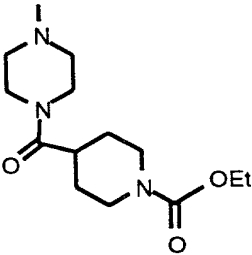
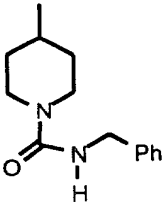
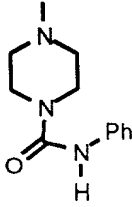
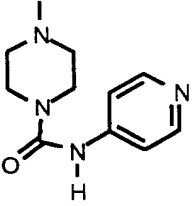
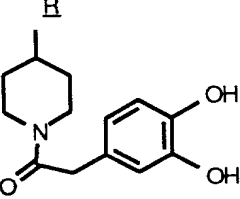
| EXAMPLE | R   | FPT IC <sub>50</sub> (μM) |
|---------|---|---------------------------|
| 316     |    | 1.26                      |
| 317     |    | 13.3                      |
| 318     |   | 4.1                       |
| 182     |  | 1.09                      |
| 183     |  | 0.97<br>0.90              |
| 321     |  | 6                         |

TABLE 10 - continued

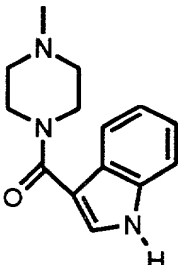
| EXAMPLE | R   | FPT IC <sub>50</sub> (μM) |
|---------|---|---------------------------|
| 368     |  | 14 @ 12μM                 |

Table 11 lists FPT IC<sub>50</sub> results for additional compounds.

5

TABLE 11

| EXAMPLE        | FPT IC <sub>50</sub><br>(μM) | EXAMPLE        | FPT IC <sub>50</sub><br>(μM) | EXAMPLE       | FPT IC <sub>50</sub><br>(μM) |
|----------------|------------------------------|----------------|------------------------------|---------------|------------------------------|
| 187<br>(6.7)   | 1.34                         | 187<br>(6.8)   | 0.95                         | 188<br>(6.9)  | 4.6                          |
| 189<br>(5.62)  | 2.44                         | 190<br>(5.63)  | 3.3                          | 191<br>(5.64) | 4.9                          |
| 192<br>(5.65)  | 1.24                         | 194<br>(5.67)  | 4.3                          | 195<br>(5.68) | 6.8                          |
| 196<br>(5.69)  | 0.36                         | 197<br>(5.70)  | 1.17                         | 198<br>(5.71) | 0.85                         |
| 199<br>(5.72A) | 10.8                         | 199<br>(5.72B) | 10.2                         | 200<br>(5.73) | 0.87                         |
| 201<br>(5.74)  | 1.4                          | 202<br>(5.75)  | 20% @<br>11μM                | 203<br>(5.76) | 11.3                         |
| 205<br>(5.78)  | 3.1                          | 206<br>(5.79)  | 1.19                         | 207<br>(5.80) | 40% @<br>12μM                |
| 208<br>(5.81)  | 4.80                         | 209<br>(5.82)  | 7.92                         | 210<br>(5.83) | 7.93                         |
| 211<br>(5.84)  | 8.17                         | 212<br>(5.85)  | 7.92                         | 213<br>(5.86) | 23% @<br>10μM                |
| 214<br>(5.87)  | 0% @<br>10μM                 | 215<br>(5.88)  | 30% @<br>13μM                | 216<br>(5.89) | 34% @<br>10μM                |

TABLE 11 - continued

| EXAMPLE        | FPT IC <sub>50</sub><br>(μM) | EXAMPLE        | FPT IC <sub>50</sub><br>(μM) | EXAMPLE        | FPT IC <sub>50</sub><br>(μM) |
|----------------|------------------------------|----------------|------------------------------|----------------|------------------------------|
| 217<br>(5.90)  | 6.75                         | 218<br>(5.91)  | 9.92                         | 233<br>(5.108) | 0.67                         |
| 251<br>(5.127) | 0.76                         | 261<br>(6.12)  | 1.3                          | 351            | 0.17                         |
| 352            | 0.74                         | 353            | 0.76                         | 354            | 0.21                         |
| 355            | 0.88                         | 273<br>(5.143) | 0.84                         | 267<br>(6.17)  | 1.33                         |
| 356            | 0.062<br>0.073               | 264<br>(6.15)  | 26% @<br>3.8μM               | 262<br>(6.13)  | 0.82                         |
| 263<br>(6.14)  | 9.8                          | 253<br>(5.129) | 4.3                          | 350            | 2.1                          |
| 252<br>(5.128) | 7.2                          | 182<br>(6.4)   | 1.09                         | 268<br>(5.139) | 1.22                         |
| 277<br>(6.20)  | 2.3                          | 193            | 7.4                          | 204            | 13.3                         |
| 355            | 0.88                         | 352            | 0.74<br>0.38                 | 353            | 0.76<br>0.30                 |

The compounds listed in Table 12 refer to compounds of Formula 525.00:

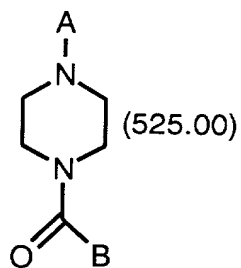
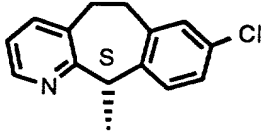
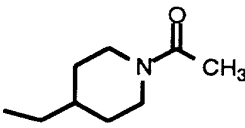
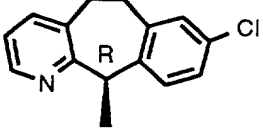
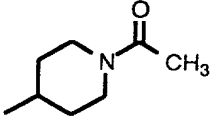
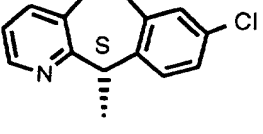
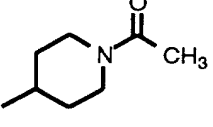
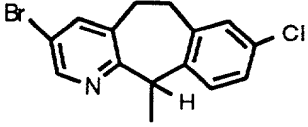
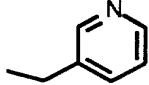
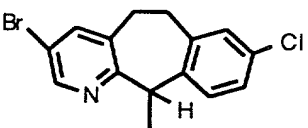
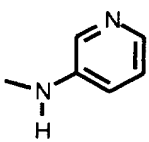


TABLE 12

| EXAMPLE    | A | B | FPT<br>IC <sub>50</sub><br>(μM) |
|------------|---|---|---------------------------------|
| 184 (5.60) |   |   | 0.91                            |
| 185 (5.61) |   |   | 3.8                             |
| 223 (5.96) |   |   | 2.1                             |
| 223 (5.97) |   |   | 0.19<br>0.72<br>0.61            |
| 224 (6.10) |   |   | 3.2                             |
| 224 (6.11) |   |   | 0.46                            |
| 225 (5.98) |   |   | 3.5                             |



TABLE 12 - continued

| EXAMPLE     | A   | B   | FPT<br>IC <sub>50</sub><br>(μM) |
|-------------|---|---|---------------------------------|
| 225 (5.99)  |    |     | 1.6                             |
| 226 (5.100) |    |     | 4.1                             |
| 226 (5.101) |    |     | 1.8                             |
| 351         |   |   | 0.17                            |
| 354         |  |  | 0.21                            |

The compounds listed in Table 13 refer to compounds of Formula 515.00:

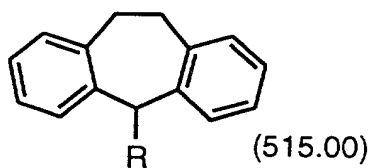
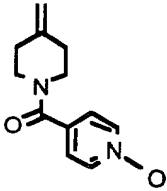
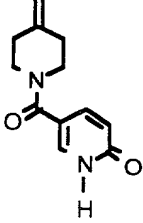
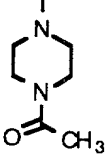
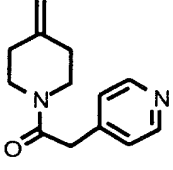


TABLE 13

| EXAMPLE | R   | FPT IC <sub>50</sub> (μM) |
|---------|---|---------------------------|
| 151     |              | 15.0                      |
| 152     |              | 15.0                      |
| 153     |              | 29.6                      |
| 87      | <br>(5.24) | 1.14                      |

Additional FPT IC<sub>50</sub> results were: (1) Example 180, compound 5.47, 0.072 μM; (2) Example 181, compound 5.48, 0.23 μM; (3) Example 182, compound 6.4, 1.09 μM; and (4) Example 183, compound 6.5, 0.97 μM.

Tables 20-22 disclose FPT Inhibition data for additional compounds.

TABLE 20

| EXAMPLE       | FPT IC <sub>50</sub> (μM) | EXAMPLE       | FPT IC <sub>50</sub> (μM) |
|---------------|---------------------------|---------------|---------------------------|
| 400 (5.210)   | 0.068                     | 401 (5.209)   | 0.063                     |
| 400-B (5.203) | 0.068                     | 400-C (5.200) | 0.08                      |
| 400-D (5.217) | 0.21                      | 400-E (5.208) | 0.030                     |
| 400-F (5.201) | 0.036                     | 400-G (5.204) | 0.04                      |
| 400-H (5.220) | 0.24                      | 400-J (5.212) | 0.024                     |
| 400-K (5.218) | 0.21                      | 400-L (5.206) | 0.14                      |
|               |                           |               | 0.095                     |
|               |                           |               | 0.09                      |

TABLE 21

| EXAMPLE     | FPT IC <sub>50</sub> (μM) | EXAMPLE       | FPT IC <sub>50</sub> (μM)           |
|-------------|---------------------------|---------------|-------------------------------------|
| 411         | 0.32                      | 411-A         | 0.59                                |
| 411-B       | 0.32                      | 402-A         | 0.45<br>0.56                        |
| 411-D       | 0.62                      | 411-E         | 1.14                                |
| 411-F       | 1.28                      | 411-G         | 0.7                                 |
| 411-L       | 0.82                      | 402           | 1.0                                 |
| 405         | 1.3                       | 406           | 1.4                                 |
| 413         | 0.103                     | 414-A         | 1.90                                |
| 414         | 0.90                      | 417           | 1.16                                |
| 418         | 1.85                      | 417-A         | 0.85                                |
| 417-B       | 0.14                      | 419           | < 0.12                              |
| 420         | 0.23                      | 422           | 0.60                                |
| 423         | >4.3<br>35 (4.3)          | 422-A         | >1.2<br>22 (1.2)                    |
| 411-N       | ~ 2<br>44 (1.3)           | 411-M         | 0.65                                |
| 411-R       | ~ 4<br>29 (1.30)          | 411-S         | 2.1                                 |
| 411-P       | 3.8                       | 411-Q         | ~ 10<br>33 (4.3)                    |
| 411-O       | ~ 5<br>39 (4)             | 411-X         | 0.45                                |
| 411-V       | 0.27                      | 411-T         | 0.58                                |
| 411-W       | 0.16<br>0.17              | 411-U         | 1.12                                |
| 425         | 1.74                      | 425-B         | 0.74                                |
| 425-A       | 2.2                       | 425-C         | 1.26                                |
| 425-E       | 0.49                      | 425-D         | 1.2                                 |
| 425-G       | 2.3                       | 425-F         | 7                                   |
| 426 (5.207) | 0.012                     | 425-H (5.202) | 0.059<br>0.059<br>0.049<br>0.075 bv |

|        |                 |               |  |
|--------|-----------------|---------------|--|
| 425-J  | 0.39            | 425-K         | 0.40<br>0.41                               |
| 425-L  | 4.5             | 426-A         | 0.33                                       |
| 427    | 1.8             | 427-A         | 2.2  |
| 425-N  | 0.64            | 428           | 1.25                                       |
| 429    | 1.27            | 425-M         | 1.8  |
| 431    | 0.82            | 431-C         | 0.88                                       |
| 431-B  | 0.92            | 431-D         | 1.0  |
| 431-A  | 1.05            | 430           | 1.3  |
| 431-E  | 0.88            | 425-O (5.126) | 0.17<br>0.14<br>0.122<br>0.118<br>0.178 bv |
| 425-P  | 0.45            | 425-Q         | 1.37                                       |
| 425-S  | 0.6             | 425-R         | 1.7  |
| 428-A  | 1.1             | 431-F         | 1.75                                       |
| 430-A  | 7               | 431-G         | 7  |
| 425-T  | 12.2            | 425-U (5.211) | 0.10<br>0.14                               |
| 425-V  | 1.66            | 434           | 0.26<br>70 (0.48)                          |
| 434-A  | 3.5             | 435           | 7.0  |
| 437    | 1000<br>36 (11) | 411-Z         | 1.5  |
| 427-B  | 0.21            | 427-C         | 0.24                                       |
| 432    | 0.66            | 415           | >3.8                                       |
| 411-C  | 6.0             | 400-M         | 0.9  |
| 411-DD | 3.1             | 411-EE        | 10 (3.3)                                   |
| 411-FF | 1.8             |               |  |

TABLE 22

| EXAMPLE | FPT IC <sub>50</sub> (μM) | EXAMPLE | FPT IC <sub>50</sub> (μM) |
|---------|---------------------------|---------|---------------------------|
| 410     | 0.70                      | 410-A   | 0.086                     |
| 410-B   | 0.084                     | 410-C   | 0.052                     |
| 410-D   |                           | 410-E   | 1000<br>31 (4.5)          |
| 410-F   | 2.2                       | 410-G   | 0.21                      |
| 410-H   | 7                         | 410-J   | 1.9                       |
| 412     | 0.52                      | 410-L   | 2.9                       |
| 403     | 1000<br>15 (12)           | 404     | 4.6                       |
| 401-A   | 1.7                       | 400-A   | 2.6                       |
| 412     | 0.52                      | 416     | 3.7                       |
| 410-M   | ~12<br>27 (3.6)           | 424     | 1.3                       |
| 424-A   | 1000<br>22 (4)            | 433     | 2.5                       |
| 433-A   | 1.1                       | 433-B   | 1.89                      |
| 433-C   | 2.5                       | 436     | 17                        |
| 436-A   | 1000<br>17 (9.6)          | 436-B   | 1000<br>2 (10.6)          |
| 436-C   | 1000<br>36 (10)           | 436-D   | 0.75                      |
| 410-S   | 1000<br>32 (3.4)          | 410-T   | 1.8                       |
| 410-U   | 5<br>40 (3.3)             | 410-V   | 1.17                      |
| 410-W   | 1.16                      |         |                           |

TABLE 14  
COMPARISON OF FPT INHIBITION AND GGPT INHIBITION

| EXAMPLE | ENZYME INHIBITION<br>FPT IC <sub>50</sub> μM | ENZYME INHIBITION<br>GGPT IC <sub>50</sub> μM |
|---------|--|---|
| 1       | 0.25   | >46   |
| 2       | 0.47   | >46   |
| 3       | 0.66   | >39   |
| 5       | 1.7  | >46   |
| 7       | 2.3  | >45   |
| 8       | 2.3  | 42  |
| 181     | 0.23   | >42   |
| 78      | 2.19<br>0.53<br>0.74<br>0.76<br>0.97         | >46   |
| 77      | 2.04   | >39   |
| 79      | 2.5  | >50   |
| 76      | 0.82   | >40   |

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TABLE 23  
COMPARISON OF FPT INHIBITION AND GGPT INHIBITION

| EXAMPLE | ENZYME INHIBITION<br>FPT IC <sub>50</sub> μM | ENZYME INHIBITION<br>GGPT IC <sub>50</sub> μM |
|---------|--|---|
| 400-D   | 0.21   | >38   |
| 400-C   | 0.030  | >38   |
| 400-B   | 0.068  | >38   |
| 400-E   | 0.04   | 1000<br>30 (38)                               |
| 400-F   | 0.036  | 1000<br>0 (36)                                |
| 400-G   | 0.024  | >39   |
| 400-H   | 0.24   | 1000<br>0 (36)                                |

|       |  |                 |
|-------|--|-----------------|
| 400-J | 0.14                                       | 1000<br>6 (36)  |
| 400-K | 0.21                                       | 1000<br>0 (37)  |
| 400   | 0.068                                      | 1000<br>29 (36) |
| 401   | 0.063<br>0.08                              | 1000<br>7 (34)  |
| 413   | 0.103                                      | >35             |
| 417-B | 0.14                                       | 1000<br>15 (32) |
| 419   | <0.12                                      | 1000<br>0 (41)  |
| 411-W | 0.16<br>0.17                               | 1000<br>3 (42)  |
| 426   | 0.012                                      | >39             |
| 425-H | 0.059<br>0.059<br>0.049<br>0.075 bv        | >38             |
| 425-O | 0.17<br>0.14<br>0.122<br>0.118<br>0.178 bv | >38             |
| 425-U | 0.10<br>0.14                               | >38             |
| 400-L | 0.095<br>0.09                              | 38              |

TABLE 24  
COMPARISON OF FPT INHIBITION AND GGPT INHIBITION

| EXAMPLE | ENZYME INHIBITION<br>FPT IC <sub>50</sub> μM | ENZYME INHIBITION<br>GGPT IC <sub>50</sub> μM |
|---------|--|---|
| 410-G   | 0.21   | 1000<br>32 (33)                               |
| 410-A   | 0.086  | ~ 40<br>47 (35)                               |
| 410-B   | 0.084  | 1000<br>21 (35)                               |

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TABLE 15  
ACTIVITY IN COS CELLS

| Example    | Inhibition of Ras<br>Processing<br>IC <sub>50</sub> (μM) | Example    | Inhibition of Ras<br>Processing<br>IC <sub>50</sub> (μM) |
|------------|--|------------|--|
| 1          | 1.0  | ----       | ----   |
| 82         | 1.2  | 156 (5.46) | 2.7  |
| 75         | 3.7  | 2          | 3.7  |
| 45         | 4.2  | 157        | 4.5  |
| 78         | <4.6   | 42         | 5.8  |
| 19         | 6.2  | 89         | 6.3  |
| 83         | 7.4  | 5          | 9.2  |
| 77         | 9.2  | 43         | 9.7  |
| 6          | 10.0   | 49         | 10.7   |
| 47         | 11.1   | 44         | 11.6   |
| 87         | 12.7   | 46         | >8.0   |
| 85         | >37.4  | 84         | >9.7   |
| 3          | >10  | 76         | 39.9   |
| 154 (5.28) | >10.0  | 48         | 10.7   |
| 5          | >12  | 88         | >12  |
| 53         | >13  | 181 (5.48) | 1.1  |
| 278        | 2.6  | 274        | 8.0  |



In Table 15, the numbers in parenthesis in the Example column refer to the formula number for the compound used in the indicated example. Also, the compound of Example 157 is:

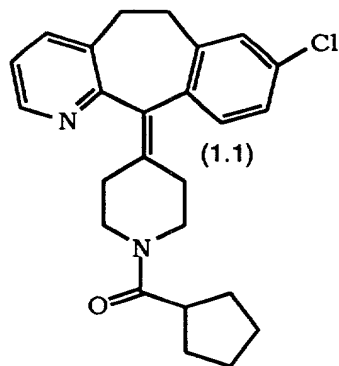


TABLE 25 - ACTIVITY IN COS CELLS

| Example | Inhibition of Ras Processing<br>IC <sub>50</sub> (μM) | Example | Inhibition of Ras Processing<br>IC <sub>50</sub> (μM) |
|---------|---|---------|---|
| 411     | ~ 1<br>93 (5)   | 411-A   | 0.7   |
| 411-B   | 1.8   | 411-D   | 1.6   |
| 400-D   | 2.0   | 400-C   | 0.7   |
| 402     | > 10  | 411-G   | 5.1   |
| 400-G   | 0.58  | 400-H   | 2.5<br>100 (5)  |
| 400-K   | 2.2<br>100 (5)  | 411-B   | 1.8   |
| 400-D   | 2.0   | 400-C   | 0.7   |
| 400-G   | 0.58  | 413     | 1.5   |
| 417     | 4.0   | 418     | >10   |
| 425-E   | 5.0   | 426     | 0.38  |
| 425-H   | 0.63<br>0.45  | 425-J   | 5.0   |
| 425-K   | 0.45  | 426-A   | > 5.0   |
| 425-O   | 0.1<br>tox (10)<br>0.4                                | 425-P   | 5.7   |
| 425-U   | 0.45<br>tox (10)                                      | 434     | <<5   |
| 400-L   | 0.6<br>0.65   |         |   |

TABLE 26  
ACTIVITY IN COS CELLS

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| Example | Inhibition of Ras Processing<br>IC <sub>50</sub> (μM) | Example | Inhibition of Ras Processing<br>IC <sub>50</sub> (μM) |
|---------|---|---------|---|
| 410-G   | 4.0   | 410-D   | 18.5  |

TABLE 16  
INHIBITION OF TUMOR CELL GROWTH  
MAT ASSAY

| Example    | Tumor<br>IC <sub>50</sub><br>(μM) | Normal<br>IC <sub>50</sub><br>(μM) | Example    | Tumor<br>IC <sub>50</sub><br>(μM) | Normal<br>IC <sub>50</sub><br>(μM) |
|------------|-----------------------------------|------------------------------------|------------|-----------------------------------|------------------------------------|
| 75         | 2.5                               | >50.0                              | ----       | ----                              | ----                               |
| 1          | 3.1                               | 25.0                               | 82         | 3.1                               | 40.0                               |
| 5          | 6.3                               | >50.0                              | 89         | 6.3                               | >25.0                              |
| 127        | 6.3                               | >50.0                              | 45         | 6.3                               | >50.0                              |
| 88         | 8.0                               | >50.0                              | 6          | 12.5                              | 50.0                               |
| 49         | 12.5                              | >50.0                              | 47         | 12.5                              | >50.0                              |
| 48         | 12.5                              | 25.0                               | 79         | 12.5                              | >50.0                              |
| 158 (5.36) | 12.5                              | 18.0                               | 2          | 25.0                              | >50.0                              |
| 10         | 25.0                              | >50.0                              | 128        | 25.0                              | >50.0                              |
| 44         | 25.0                              | 25.0                               | 164 (5.30) | 25.0                              | >50.0                              |
| 43         | 25.0                              | 50.0                               | 165 (5.34) | 25.0                              | 50.0                               |
| 53         | 25.0                              | >50.0                              | 166 (5.26) | 37.0                              | >50.0                              |
| 159 (5.31) | 37.0                              | >50.0                              | 167 (5.32) | 37.0                              | 50.0                               |
| 160 (5.39) | 37.0                              | 50.0                               | 168 (5.44) | 37.0                              | >50.0                              |
| 161 (5.45) | 37.0                              | >50.0                              | 5          | 37.5                              | 100.0                              |
| 162 (5.29) | 37.0                              | >50.0                              | 93         | 40.0                              | >50.0                              |
| 94         | 40.0                              | 80.0                               | 88         | >50.0                             | >50.0                              |
| 3          | >50.0                             | >50.0                              | 7          | 50.0                              | 100.0                              |
| 90         | 50.0                              | >50.0                              | 91         | 50.0                              | 80.0                               |
| 95         | >50.0                             | >50.0                              | 11         | >50.0                             | >50.0                              |
| 12         | 50.0                              | >50.0                              | 96         | 50.0                              | >50.0                              |
| 97         | >50.0                             | >50.0                              | 98         | 50.0                              | >50.0                              |
| 121        | 50.0                              | >50.0                              | 126        | 50.0                              | >50.0                              |
| 163 (5.27) | 50.0                              | >50.0                              | 42         | 50.0                              | >50.0                              |
| 154 (5.28) | >50.0                             | >50.0                              | 169 (5.33) | >50.0                             | >50.0                              |
| 46         | 50.0                              | >50.0                              | 80         | >50.0                             | >50.0                              |
| 77         | >50.0                             | >50.0                              | 76         | >50.0                             | >50.0                              |
| 81         | >50.0                             | >50.0                              | 173 (5.35) | >50.0                             | >50.0                              |

TABLE 16 - continued

| Example    | Tumor<br>IC <sub>50</sub><br>(μM) | Normal<br>IC <sub>50</sub><br>(μM) | Example    | Tumor<br>IC <sub>50</sub><br>(μM) | Normal<br>IC <sub>50</sub><br>(μM) |
|------------|-----------------------------------|------------------------------------|------------|-----------------------------------|------------------------------------|
| 170 (5.37) | 50.0                              | >50.0                              | 174 (5.38) | 50.0                              | 50.0                               |
| 171 (5.40) | 50.0                              | >50.0                              | 87         | 50.0                              | >50.0                              |
| 172 (5.42) | >50.0                             | >50.0                              | 175 (5.43) | >50.0                             | >50.0                              |
| 180 (5.47) | 18                                | >50.0                              | 181 (5.48) | <3.1                              | >50.0                              |

In Table 16, the numbers in parenthesis in the Example column refer to the formula number for the compound used in the indicated example.

5

TABLE 27  
INHIBITION OF TUMOR CELL GROWTH  
MAT ASSAY

10

| Example | Tumor<br>IC <sub>50</sub><br>(μM) | Normal<br>IC <sub>50</sub><br>(μM) | Example | Tumor<br>IC <sub>50</sub><br>(μM) | Normal<br>IC <sub>50</sub><br>(μM) |
|---------|-----------------------------------|------------------------------------|---------|-----------------------------------|------------------------------------|
| 411-A   | 1.6                               | > 25                               | 411     | 18                                | > 25                               |
| 411-B   | 6.25                              | >25                                | 402-A   | 3.1                               | >25                                |
| 411-D   | 8                                 | >25                                | 411-E   | >25                               | >25                                |
| 400-D   | 4                                 | >25                                | 400-C   | <1.6                              | >25                                |
| 402     | 18                                | >25                                | 400-B   | <1.6                              | 6.25                               |
| 411-G   | 6.25<br>4                         | >25<br>>12.5                       | 400-E   | <1.6                              | 18                                 |
| 400-F   | <1.6                              | >25                                | 405     | 12.5                              | >25                                |
| 400-G   | 1.6                               | >25                                | 400     | 1.6                               | >25                                |
| 401     | <1.6                              | >25                                | 411-B   | 6.25                              | >25                                |
| 402-A   | 3.1                               | >25                                | 400-D   | 4                                 | >25                                |
| 400-C   | <1.6                              | >25                                | 400-B   | <1.6                              | >25                                |
| 400-G   | 1.6                               | >25                                | 413     | >6.25                             | 10                                 |
| 417     | 10                                | 18                                 | 418     | 25                                | >25                                |
| 417-B   | <1.6                              | >25                                | 425     | 12.5                              | >25                                |
| 425-B   | 12.5                              | >25                                | 425-E   | 1.6                               | >25                                |

|       |             |              |       |              |              |
|-------|-------------|--------------|-------|--------------|--------------|
| 426   | 3.1<br><0.8 | 25<br>>12.5  | 425-H | <1.6         | >25          |
| 425-J | 3.1         | >25          | 425-K | 6.25         | >25          |
| 426-A | 6.25        | >25          | 428   | 12.5         | 18           |
| 425-O | 3.1<br><0.8 | 6.25<br>6.25 | 425-P | >3.1         | 3.1          |
| 425-U | 6.25        | 10           | 400-L | <1.6<br><0.8 | >25<br>>12.5 |

**TABLE 28**  
**INHIBITION OF TUMOR CELL GROWTH**  
**MAT ASSAY**

5

| Example | Tumor<br>IC <sub>50</sub><br>( $\mu$ M) | Normal<br>IC <sub>50</sub><br>( $\mu$ M) | Example | Tumor<br>IC <sub>50</sub><br>( $\mu$ M) | Normal<br>IC <sub>50</sub><br>( $\mu$ M) |
|---------|---|--|---------|---|--|
| 410-D   | 10                                      | >50                                      |         |   |  |

**TABLE 17**

| Example    | Enzyme<br>Inhibition<br>GGPT<br>IC <sub>50</sub> ( $\mu$ M) | COS CELLS<br>Activity<br>Inhibition of<br>Ras<br>Processing<br>IC <sub>50</sub> ( $\mu$ M) | Inhibition of Tumor Cell<br>Growth<br>MAT Assay<br>IC <sub>50</sub> ( $\mu$ M) |        |
|------------|---|--|--|--------|
|            |   |  | Tumor  | Normal |
| 180        | >42   | 1.0  | 18   | >50    |
|            |   | 6.3  | 12.5   | 50     |
|            |   | 2.4  | 12.5   | >50    |
| 182 (6.4)  | >40   | 12.0   | 37   | >50    |
| 183 (6.5)  | >40   | 10.5   | 5  | 18     |
| 184 (5.60) | ----  | 11.5   | 12.5   | >50    |
| 185 (5.61) | ----  | >20  | ----   | ----   |
| 187 (6.7)  | >46   | 4.8  | 37   | >50    |
|            |   |  | 25   | >50    |

TABLE 17 - continued

| Example    | Enzyme<br>Inhibition<br>GGPT<br>IC <sub>50</sub> (μM) | COS CELLS<br>Activity<br>Inhibition of<br>Ras<br>Processing<br>IC <sub>50</sub> (μM) | Inhibition of Tumor Cell<br>Growth<br>MAT Assay<br>IC <sub>50</sub> (μM) |            |
|------------|---|--|--|------------|
|            |   |  | Tumor  | Normal     |
| 187 (6.8)  | >46   | 1.3  | 9<br>4   | >50<br>50  |
| 189 (5.62) | 42  | 7.0  | 37   | >50        |
| 190 (5.63) | ----  | ----   | >50  | >50        |
| 191 (5.64) | ----  | ----   | <3.1   | 50         |
| 192 (5.65) | >43   | 4.9  | 25<br>37   | >50<br>>50 |
| 196 (5.69) | >46   | 5.0  | 37<br>25   | >50<br>>50 |
| 197 (5.70) | ----  | 11.1   | 25   | >50        |
| 198 (5.71) | ----  | 6.1  | 12.5   | >50        |
| 200 (5.73) | ----  | 2.7  | 18   | >50        |
| 201 (5.74) | ----  | 0.93   | 3.1  | 12.5       |
| 206        | ----  | 2.4  | <3.1   | 16         |
| 208 (5.81) | ----  | ----   | >50  | >50        |
| 209 (5.82) | ----  | ----   | 25   | >50        |
| 211 (5.84) | ----  | ----   | 37   | >50        |
| 212 (5.85) | ----  | ----   | 25   | 37         |
| 217 (5.90) | ----  | ----   | 37   | 50         |
| 218 (5.91) | ----  | ----   | 37   | 50         |
| 219 (5.92) | ----  | ----   | 25   | >50        |
| 220 (5.93) | ----  | ----   | 25   | >50        |
| 221 (5.94) | ----  | ----   | 6.25   | >50        |
| 222 (5.95) | ----  | 4.7  | 18   | 37         |
| 223 (5.96) | ----  | 10.5   | 25   | >50        |
| 223 (5.97) | ----  | 1.3  | 8  | >50        |
| 224 (6.11) | ----  | 7.3  | 37   | >50        |
| 225 (5.98) | ----  | ----   | 12.5   | 50         |

TABLE 17 - continued

| Example     | Enzyme<br>Inhibition<br>GGPT<br>IC <sub>50</sub> (μM) | COS CELLS<br>Activity<br>Inhibition of<br>Ras<br>Processing<br>IC <sub>50</sub> (μM) | Inhibition of Tumor Cell<br>Growth<br>MAT Assay<br>IC <sub>50</sub> (μM) |        |
|-------------|---|--|--|--------|
|             |   |  | Tumor  | Normal |
| 225 (5.99)  | ----  | 6.2  | 12.5   | >50    |
| 226 (5.100) | ----  | ----   | 25   | >50    |
| 226 (5.101) | ----  | 6.5  | 12.5   | >50    |
| 227 (5.102) | >41   | 1.0  | 4  | >50    |
| 229 (5.104) | ----  | ----   | 37   | >50    |
| 230 (5.105) | ----  | >20  | 37   | >50    |
| 233 (5.108) | ----  | 10   | 18   | >50    |
| 235         | ----  | 9.1  | 12.5   | >50    |
| 236 (5.111) | >45   | 3.5  | 4  | >50    |
| 237 (5.112) | ----  | ----   | >50  | >50    |
| 238 (5.113) | ----  | ----   | >50  | >50    |
| 239 (5.114) | ----  | 4.6  | 37   | >50    |
| 246 (5.121) | >40   | >3.9   | 12.5   | 50     |
|             |   | 3.1  | <3.1   | >50    |
|             |   | 0.91   |  |        |
| 247 (5.122) | >40   | >3.9   | 25   | >50    |
|             |   | 3.5  | 8  | >50    |
| 248 (5.124) | ----  | 2.05   | 18   | >50    |
| 248 (5.123) | ----  | 4.6  | 18   | >50    |
| 250 (5.126) | ----  | 8.6  | 18   | >50    |
| 251 (5.127) | ----  | 8.1  | ----   | ----   |
| 261 (6.12)  | ----  | 9.1  | ----   | ----   |
| 266 (5.138) | ----  | 0.77   | 3.1  | 6.25   |
|             |   | 0.89   |  |        |
| 267 (6.17)  | ----  | 12.5   | ----   | ----   |
| 269 (5.140) | ----  | 0.69   | 6.25   | 12.5   |
| 276 (5.145) | ----  | 2.9  | 12.5   | 50     |
| 281 (5.149) | ----  | 7.0  | 4  | >50    |

TABLE 17 - continued

| Example     | Enzyme<br>Inhibition<br>GGPT<br>IC <sub>50</sub> (μM) | COS CELLS<br>Activity<br>Inhibition of<br>Ras<br>Processing<br>IC <sub>50</sub> (μM) | Inhibition of Tumor Cell<br>Growth<br>MAT Assay<br>IC <sub>50</sub> (μM) |                   |
|-------------|---|--|--|-------------------|
|             |   |  | Tumor  | Normal            |
| 283 (5.151) | ----  | 5.6  | 10   | >50               |
| 285 (5.153) | ----  | 5.2<br>10.1  | 12.5   | >50               |
| 286 (5.154) | ----  | 8.3  | 25   | >50               |
| 287         | >40   | >10<br>>10   | 3.1<br>50<br>25  | >50<br>>50<br>>50 |
| 288         | ----  | 2.8  | 8  | >50               |
| 289         | >40   | >10  | 12.5<br>18<br>12.5   | >50<br>>50<br>>50 |
| 290         | >38   | ----   | 12.5<br>6.25<br>8  | >50<br>>50<br>>50 |
| 291         | >46   | 3.6  | 18   | >50               |
| 292         | >44   | 6.8  | 6.25   | >50               |
| 293         | >40   | >11.1<br>6.5   | 12.5<br>12.5<br>12.5   | >50<br>>50<br>>50 |
| 294         | ----  | 5.2<br>2.8   | 18   | >50               |
| 295         | ----  | 20.8   | ----   | ----              |
| 297         | 41  | ----   | >50  | >50               |
| 298         | >35   | >9   | >50  | >50               |
| 299         | 1000  | ----   | ----   | ----              |
| 300         | ----  | 2.6  | <3.1   | >50               |
| 301         | 40  | 4.4<br>1.0   | 12.5<br><3.1<br><3.1   | >50<br>>50<br>>50 |



|     |      |             |      |      |
|-----|------|-------------|------|------|
| 303 | >43  | 3.4         | 8    | >50  |
| 304 | >40  | ----        | 50   | >50  |
| 305 | ---- | ----        | 25   | >50  |
| 307 | ---- | 4.6<br>0.85 | 12.5 | 50   |
| 309 | 35.1 | >10         | ---- | ---- |
| 310 | ---- | ----        | 25   | >50  |

TABLE 17 continued

| Example | Enzyme<br>Inhibition<br>GGPT<br>IC <sub>50</sub> (μM) | COS CELLS<br>Activity<br>Inhibition of<br>Ras<br>Processing<br>IC <sub>50</sub> (μM) | Inhibition of Tumor Cell<br>Growth<br>MAT Assay<br>IC <sub>50</sub> (μM) |        |
|---------|---|--|--|--------|
|         |   |  | Tumor  | Normal |
| 311     | 41.3  | 9.5  | 10   | >50    |
| 312     | >46   | 3.8  | 12.5   | >50    |
| 313     | >46   | 1.5  | 6.25   | >50    |
| 314     | >46   | 3.0  | 4  | >50    |
| 234     | >43   | 2.2  | 3.1  | >50    |
| 316     | >43   | 18.4   | 25   | >50    |
| 318     | ----  | ----   | 37   | 37     |
| 321     | ----  | ----   | 6.25   | >50    |
| 322     | ----  | 2.8  | 8  | >50    |
| 351     | 1000  | 2.8  | 6.25   | 25     |
| 354     | 1000  | ----   | 6.25   | ≥25    |
| 365     | ----  | 3.1  | 6.25   | >50    |
| 366     | ----  | 3.3  | 3.1  | >50    |
| 367     | ----  | 6.2  | 6.25   | >50    |
| 78      | >46   | ----   | ----   | ----   |
| 77      | >39   | ----   | ----   | ----   |
| 79      | >50   | 5.1  | ----   | ----   |
| 76      | >50   | ----   | ----   | ----   |
| 350     | ----  | 3.7  | ----   | ----   |
| 355     | ----  | 0.89   | 8  | >25    |

|     |      |     |      |     |
|-----|------|-----|------|-----|
| 352 | ---- | 2.2 | 1.6  | >25 |
| 353 | ---- | 0.9 | 6.25 | >25 |

## RESULTS:

### 1. Enzymology:

5 The data demonstrate that the compounds of the invention are inhibitors of Ras-CVLS farnesylation by partially purified rat brain farnesyl protein transferase (FPT). The data also show that there are compounds of the invention which can be considered as potent ( $IC_{50} < 10 \mu M$ ) inhibitors of Ras-CVLS farnesylation by partially purified rat brain FPT.

10 The data also demonstrate that compounds of the invention are poorer inhibitors of geranylgeranyl protein transferase (GGPT) assayed using Ras-CVLL as isoprenoid acceptor. Generally, the compounds of the invention are inactive or weakly active as geranylgeranyl transferase inhibitors at  $20 \mu g/mL$ . For example, with reference to Table 14, the compound of Example 1 inhibits GGPT 24% at  $46 \mu M$  and is at least 184-  
15 fold selective for FPT inhibition. The compound of Example 2, for example, inhibits GGPT 25% at  $46 \mu M$  and is at least 98-fold selective for FPT inhibition. For another example, the compound of Example 3 inhibits GPPT 3% at  $39 \mu M$  and is at least 59-fold selective for FPT. This selectivity is important for the therapeutic potential of the compounds used  
20 in the methods of this invention, and increases the potential that the compounds will have selective growth inhibitory properties against Ras-transformed cells.

### 2. Cell-Based: COS Cell Assay

25 Western blot analysis of the Ras protein expressed in Ras-transfected COS cells following treatment with the tricyclic farnesyl protein transferase inhibitors of this invention indicated that they inhibit Ras-CVLS processing, causing accumulation of unprocessed Ras (see Table 15). The compound of Example 1, for example, inhibited Ras-CVLS processing with an  $IC_{50}$  value of  $1 \mu M$  ( $0.44 \mu g/mL$ ), but did not block the  
30 geranylgeranylation of Ras-CVLL at concentrations up to  $20 \mu g/mL$ . Microscopic and photographic examination of the Ras-transfected COS cells following treatment with two of the tricyclic farnesyl transferase inhibitors of this invention indicated that they also blocked phenotypic changes induced by expression of oncogenic Ras. Cells expressing  
35 oncogenicRas-CVLS or Ras-CVLL overgrew the monolayer and formed

dense foci of cells. The compound of Example 1 inhibited the morphological changes induced by Ras-CVLS in a dose-dependent manner over the concentration range of 2 to 20  $\mu\text{g/mL}$ . The compound of Example 1 had little effect at 0.2 or 0.5  $\mu\text{g/mL}$ . Importantly, 20  $\mu\text{g/mL}$  of the compound of Example 1 did not prevent the morphological changes induced by Ras-CVLL.

These results provide evidence for specific inhibition of farnesyl protein transferase, but not geranylgeranyl transferase I, by compounds of this invention in intact cells and indicate their potential to block cellular transformation by activated Ras oncogenes.

### 3. Cell-Based: Cell Mat Assay

Tricyclic farnesyl protein transferase inhibitors of this invention also inhibited the growth of Ras-transformed tumor cells in the Mat assay without displaying cytotoxic activity against the normal monolayer.

### In Vivo Anti-Tumor Studies:

Tumor cells ( $5 \times 10^5$  to  $8 \times 10^6$  of M27 (mouse Lewis lung carcinoma), A431 (human epidermal carcinoma) or SW620 (human colon adenocarcinoma [lymph node metastasis])) are inoculated subcutaneously into the flank of 5-6 week old athymic nu/nu female mice. For the C-f-1 (mouse fibroblast transformed with c-fos oncogene) tumor model, 2  $\text{mm}^3$  tumor fragments are transplanted subcutaneously into the flank of 5-6 week old athymic nu/nu female mice. Tumor bearing animals are selected and randomized when the tumors are established. Animals are treated with vehicle (beta cyclodextran for i.p. or corn oil for p.o.) only or compounds in vehicle twice a day (BID) for 5 (1-5), 6 (1-6), or 7 (1-7) days per week for 2 (x2) or 4 (x4) weeks. The percent inhibition of tumor growth relative to vehicle controls are determined by tumor measurements. The results are reported in Table 18.

**TABLE 18**  
**In-Vivo Anti-Tumor Results**

| s.c.<br>Tumor | Route &<br>Schedule | Ex<br>2 | Ex<br>1 | Ex<br>3 | Ex<br>7 | Ex<br>78 | Ex<br>79 | Ex<br>75 |
|---------------|---------------------|---------|---------|---------|---------|----------|----------|----------|
| M27           | po, BID,<br>1-7, x4 | 61.2    | -----   | 27.3    | 58.2    | -----    | -----    | -----    |
| A431          | ip, BID,<br>1-5, x4 | -----   | 20.5    | 0       | 0       | -----    | -----    | -----    |
| A431          | po, BID<br>1-5, x4  | 45.6    | -----   | 8       | 29.1    | -----    | -----    | -----    |
| A431          | po, BID,<br>1-5, x4 | 36.5    | -----   | 26      | -----   | -----    | -----    | -----    |
| A431          | po, BID,<br>1-6, x4 | -----   | -----   | -----   | -----   | 31       | 0        | 34.5     |
| C-f-1         | ip, BID,<br>1-5, x2 | 8       | 0       | 8       | 39.7    | -----    | -----    | -----    |
| C-f-1         | po, BID,<br>1-5, x4 | 9.6     | -----   | 0       | 39.3    | -----    | -----    | -----    |
| C-f-1         | po, BID,<br>1-5, x4 | -----   | -----   | -----   | -----   | 26.7     | 25       | 20       |
| SW-<br>620    | ip, BID,<br>1-5, x4 | 0       | 0       | 27      | 19.6    | -----    | -----    | -----    |
| SW-<br>620    | po, BID,<br>1-5, x2 | 46.1    | 0       | 15.8    | 48.6    | -----    | -----    | -----    |

**TABLE 18 - continued**

5

| s.c.<br>Tumor | Route &<br>Schedule | Ex<br>2 | Ex<br>1 | Ex<br>3 | Ex<br>7 | Ex<br>78 | Ex<br>79 | Ex<br>75 |
|---------------|---------------------|---------|---------|---------|---------|----------|----------|----------|
| SW-<br>620    | po, BID,<br>1-5, x4 | 33.5    | -----   | -----   | 0       | -----    | -----    | -----    |
| SW-<br>620    | po, BID,<br>1-5, x4 | -----   | -----   | -----   | -----   | 59.6     | 26.7     | 43.4     |

Additional in-vivo anti-tumor results are reported in Table 19. In Table 23, LOX is a human melanoma cell line, and the schedule "10/wk, x4", for example, means 10 times per week (twice a day Monday to Friday) for 4 weeks.

**TABLE 19**  
**In-Vivo Anti-Tumor Results**

| Example<br>or<br>Structure | Tumor | Dose<br>(MPK) | Route &<br>Schedule | Average<br>% Tumor<br>Inhibition |
|----------------------------|-------|---------------|---------------------|----------------------------------|
| Ex. 2                      | SW620 | 100           | ip, 10/wk, x2       | 0                                |
|                            | SW620 | 100           | po, 10/wk, x2       | 0                                |
|                            | SW620 | 100           | po, 10/wk, x4       | 1                                |
|                            | M27   | 100           | po, 14/wk, x4       | 45                               |
| Ex. 4                      | SW620 | 100           | po, 10/wk, x4       | 2                                |
| Ex. 7                      | SW620 | 100           | po, 10wk, x2        | 13                               |
|                            | SW620 | 100           | po, 10/wk, x4       | 0                                |
|                            | M27   | 100           | po, 14/wk, x4       | 40                               |
| Ex. 45                     | SW620 | 100           | po, 10/wk, x4       | 0                                |
|                            | SW620 | 100           | po, 10/wk, x4       | 19                               |
|                            | M27   | 100           | po, 10/wk, x3       | 0                                |
| Ex. 47                     | SW620 | 100           | po, 10/wk, x4       | 0                                |
|                            | SW620 | 100           | po, 10/wk, x4       | 30                               |
|                            | M27   | 100           | po, 10/wk, x3       | 19                               |
| Ex. 49                     | SW620 | 100           | po, 10/wk, x4       | 0                                |
|                            | SW620 | 100           | po, 10/wk, x4       | 27                               |
|                            | M27   | 100           | po, 10/wk, x3       | 30                               |

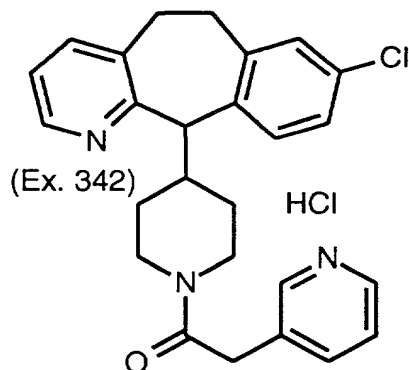
TABLE 19 - continued

| Example<br>or<br>Structure | Tumor | Dose<br>(MPK) | Route &<br>Schedule | Average<br>% Tumor<br>Inhibition |
|----------------------------|-------|---------------|---------------------|----------------------------------|
| Ex. 75                     | SW620 | 100           | po, 10/wk, x4       | 26                               |
|                            | SW620 | 100           | po, 10/wk, x4       | 4                                |
|                            | SW620 | 100           | po, 10/wk, x4       | 54                               |
|                            | SW620 | 100           | po, 10/wk, x4       | 7                                |
|                            | M27   | 100           | po, 10/wk, x4       | 0                                |
| Ex. 82                     | SW620 | 100           | po, 10/wk, x4       | 25                               |
|                            | SW620 | 100           | po, 10/wk, x4       | 32                               |
| Ex. 88                     | SW620 | 100           | po, 10/wk, x4       | 43.25*                           |
|                            | M27   | 100           | po, 10/wk, x4       | 19                               |
|                            | SW620 | 100           | po, 10/wk, x4       | 38*                              |
|                            | LOX   | 100           | po, 10/wk, x4       | 70                               |
|                            | SW620 | 100           | po, 10/wk, x4       | 38                               |
|                            | SW620 | 100           | po, 10/wk, x4       | 37                               |
|                            | SW620 | 50            | po, 10/wk, x4       | 30                               |
|                            | SW620 | 50            | po, 10/wk, x4       | 30                               |
|                            | SW620 | 25            | po, 10/wk, x4       | 4                                |
|                            | SW620 | 25            | po, 10/wk, x4       | 0                                |
|                            | SW620 | 100           | po, 10/wk, x4       | 27.4*                            |
|                            | LOX   | 100           | po, 10/wk, x4       | 33                               |
|                            | SW620 | 100           | po, 10/wk, x4       | 28                               |
|                            | SW620 | 100           | po, 10/wk, x4       | 38                               |
| Ex. 127                    | SW620 | 100           | po, 10/wk, x4       | 25                               |
|                            | SW620 | 100           | po, 10/wk, x4       | 42                               |
|                            | M27   | 100           | po, 10/wk, x3       | 22                               |
| Ex. 187 (6.8)              | SW620 | 100           | po, 10/wk, x4       | 11                               |
|                            | SW620 | 100           | po, 10/wk, x4       | 21                               |
| Ex. 192                    | SW620 | 100           | po, 10/wk, x4       | 29                               |
|                            | SW620 | 100           | po, 10/wk, x4       | 40                               |
| Ex. 287                    | SW620 | 100           | po, 10/wk, x4       | 14                               |
|                            | SW620 | 100           | po, 10/wk, x4       | 0                                |
| Ex. 290                    | SW620 | 100           | po, 10/wk, x4       | 41                               |
|                            | SW620 | 100           | po, 10/wk, x4       | 16                               |

TABLE 19 - continued

| Example or Structure         | Tumor | Dose (MPK) | Route & Schedule | Average % Tumor Inhibition |
|------------------------------|-------|------------|------------------|----------------------------|
| Ex. 293                      | SW620 | 100        | po, 10/wk, x4    | 5                          |
|                              | SW620 | 100        | po, 10/wk, x4    | 47                         |
| Ex. 301                      | SW620 | 100        | po, 10/wk, x4    | 16                         |
|                              | SW620 | 100        | po, 10/wk, x4    | 0                          |
| Ex. 82A                      | SW620 | 100        | po, 10/wk, x4    | 27                         |
|                              | SW620 | 100        | po, 10/wk, x4    | 26                         |
| Ex. 342                      | SW620 | 100        | po, 10/wk, x4    | 39                         |
|                              | SW620 | 100        | po, 10/wk, x4    | 31                         |
| 5.21                         | SW620 | 100        | po, 10/wk, x4    | 19                         |
|                              | SW620 | 100        | po, 10/wk, x4    | 17                         |
|                              | M27   | 100        | po, 10/wk, x4    | 0                          |
| 5.25                         | SW620 | 100        | po, 10/wk, x4    | 7                          |
|                              | SW620 | 100        | po, 10/wk, x4    | 36                         |
| * Average of several results |       |            |                  |                            |

The compound of Example 342 (Table 19) is:



- 5 For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may be comprised of from about 5 to about 70
- 10 percent active ingredient. Suitable solid carriers are known in the art, e.g. magnesium carbonate, magnesium stearate, talc, sugar, lactose. Tablets,

powders, cachets and capsules can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides or cocoa butter is first melted, and the active ingredient is dispersed homogeneously therein as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby solidify.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection.

Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

Preferably the compound is administered orally.

Preferably, the pharmaceutical preparation is in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 0.1 mg to 1000 mg, more preferably from about 1 mg. to 300 mg, according to the particular application.

The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the



circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

The amount and frequency of administration of the compounds of the invention and the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended dosage regimen is oral administration of from 10 mg to 2000 mg/day preferably 10 to 1000 mg/day, in two to four divided doses to block tumor growth. The compounds are non-toxic when administered within this dosage range.

The following are examples of pharmaceutical dosage forms which contain a compound of the invention. The scope of the invention in its pharmaceutical composition aspect is not to be limited by the examples provided.

#### Pharmaceutical Dosage Form Examples

##### EXAMPLE A

##### Tablets

| No.   | Ingredients   | mg/tablet | mg/tablet |
|-------|---|-----------|-----------|
| 1.    | Active compound   | 100       | 500       |
| 2.    | Lactose USP   | 122       | 113       |
| 3.    | Corn Starch, Food Grade,<br>as a 10% paste in<br>Purified Water | 30        | 40        |
| 4.    | Corn Starch, Food Grade   | 45        | 40        |
| 5.    | Magnesium Stearate  | <u>3</u>  | <u>7</u>  |
| Total |   | 300       | 700       |

##### Method of Manufacture

Mix Item Nos. 1 and 2 in a suitable mixer for 10–15 minutes. Granulate the mixture with Item No. 3. Mill the damp granules through a coarse screen (e.g., 1/4", 0.63 cm) if necessary. Dry the damp granules. Screen the dried granules if necessary and mix with Item No. 4 and mix for 10–15 minutes. Add Item No. 5 and mix for 1–3 minutes. Compress the mixture to appropriate size and weigh on a suitable tablet machine.

**EXAMPLE B**  
**Capsules**

| No.   | Ingredient              | mg/capsule | mg/capsule |
|-------|-------------------------|------------|------------|
| 1.    | Active compound         | 100        | 500        |
| 2.    | Lactose USP             | 106        | 123        |
| 3.    | Corn Starch, Food Grade | 40         | 70         |
| 4.    | Magnesium Stearate NF   | <u>7</u>   | <u>7</u>   |
| Total |                         | 253        | 700        |

5 **Method of Manufacture**

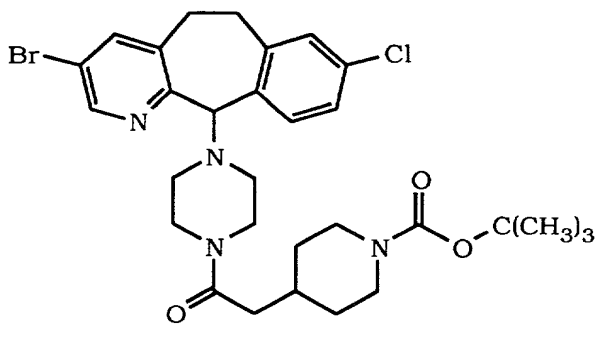
Mix Item Nos. 1, 2 and 3 in a suitable blender for 10-15 minutes. Add Item No. 4 and mix for 1-3 minutes. Fill the mixture into suitable two-piece hard gelatin capsules on a suitable encapsulating machine.

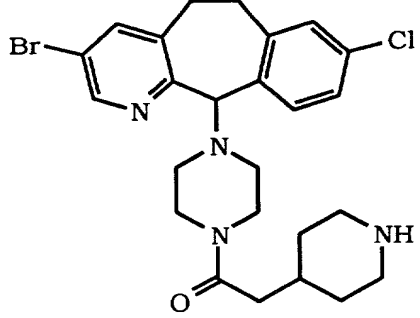
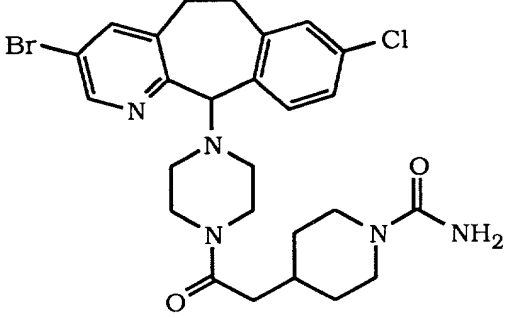
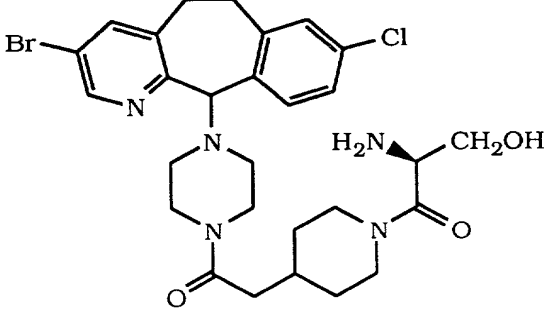
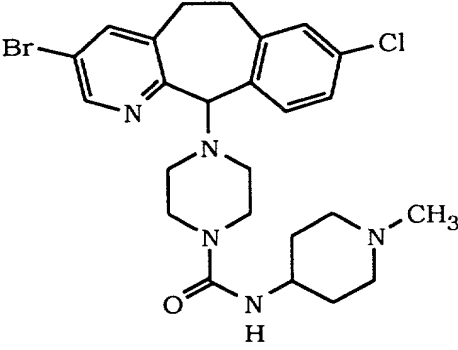
10 While the present invention has been described in conjunction with the specific embodiments set forth above, many alternatives, modifications and variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

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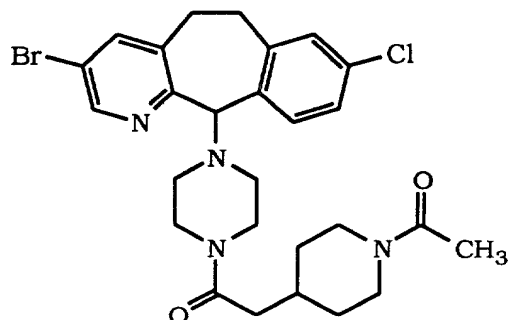
In addition to the examples provided above, the following compounds were prepared using the product of Preparative Example 40 and following substantially the same procedures as described for Examples 193, 428, 431, 433-A, and 183, as appropriate:

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| Example No. | Compound   | Analytical Data                         |
|-------------|--|---|
| 500         |  | Mass Spec.:<br>MH <sup>+</sup> = 619.15 |

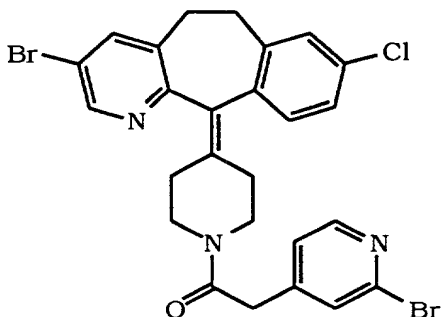
|     |  |                                |
|-----|--|--------------------------------|
| 501 |     | Mass Spec.:<br>$MH^+ = 517$    |
| 502 |    | Mass Spec.:<br>$MH^+ = 560$    |
| 503 |  | Mass Spec.:<br>$MH^+ = 604.2$  |
| 504 |  | Mass Spec.:<br>$MH^+ = 532.15$ |

EXAMPLE 505



- 5      React the compound of Example 501 with an excess of acetic anhydride in MeOH via standard procedures to form the product compound in 91% yield. Mass Spec.:  $MH^+ = 559$

EXAMPLE 506



10

React the compound of Preparative Example 49 with 4-(2-bromopyridyl)acetic acid via the substantially the same procedure as described for Example 410 to give the product compound. m.p. = 134°-136.1°C; Mass Spec.:  $MH^+ = 588$

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